Supplementary appendix:

Figure S1: Schema of venetoclax combined with CLIA

Induction								
Treatment	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Cladribine 5 mg/m²	X	X	X	X	X			
Idarubicin 10 mg/m²	X	X	X					
Ara-C 1500 mg/m²	X	X	X	X	X			
Venetoclax		X	X	X	X	X	X	X

Consolidation								
Treatment	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Cladribine 5 mg/m²	X	X	X					
Idarubicin 8 mg/m²	X	X						
Ara-C 1000 mg/m²	X	X	X					
Venetoclax		X	X	X	X	X	X	X

Figure S2: Oncoprint of mutations in individual patients.

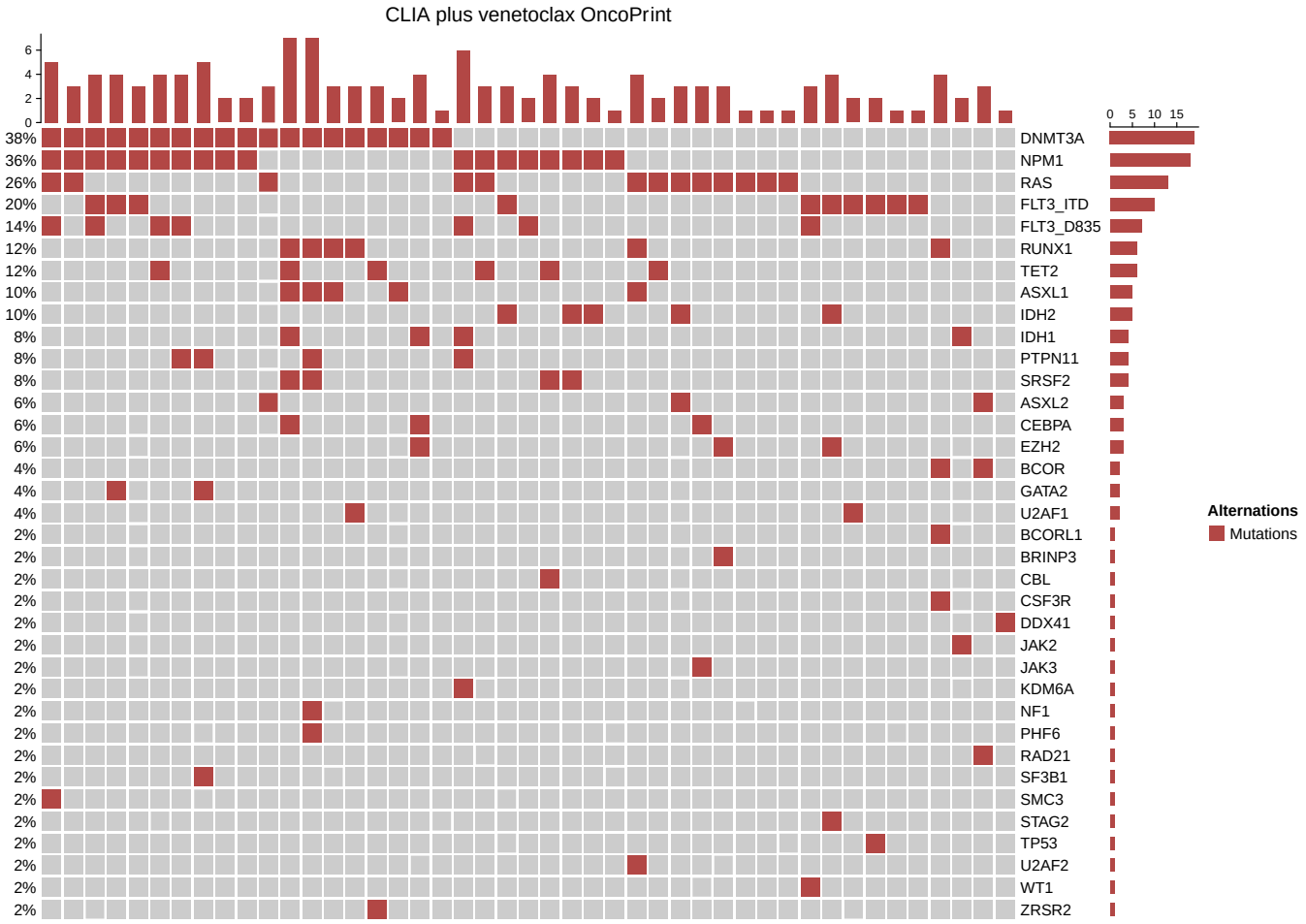


Figure S3: Duration of response Kaplan-Meier curve

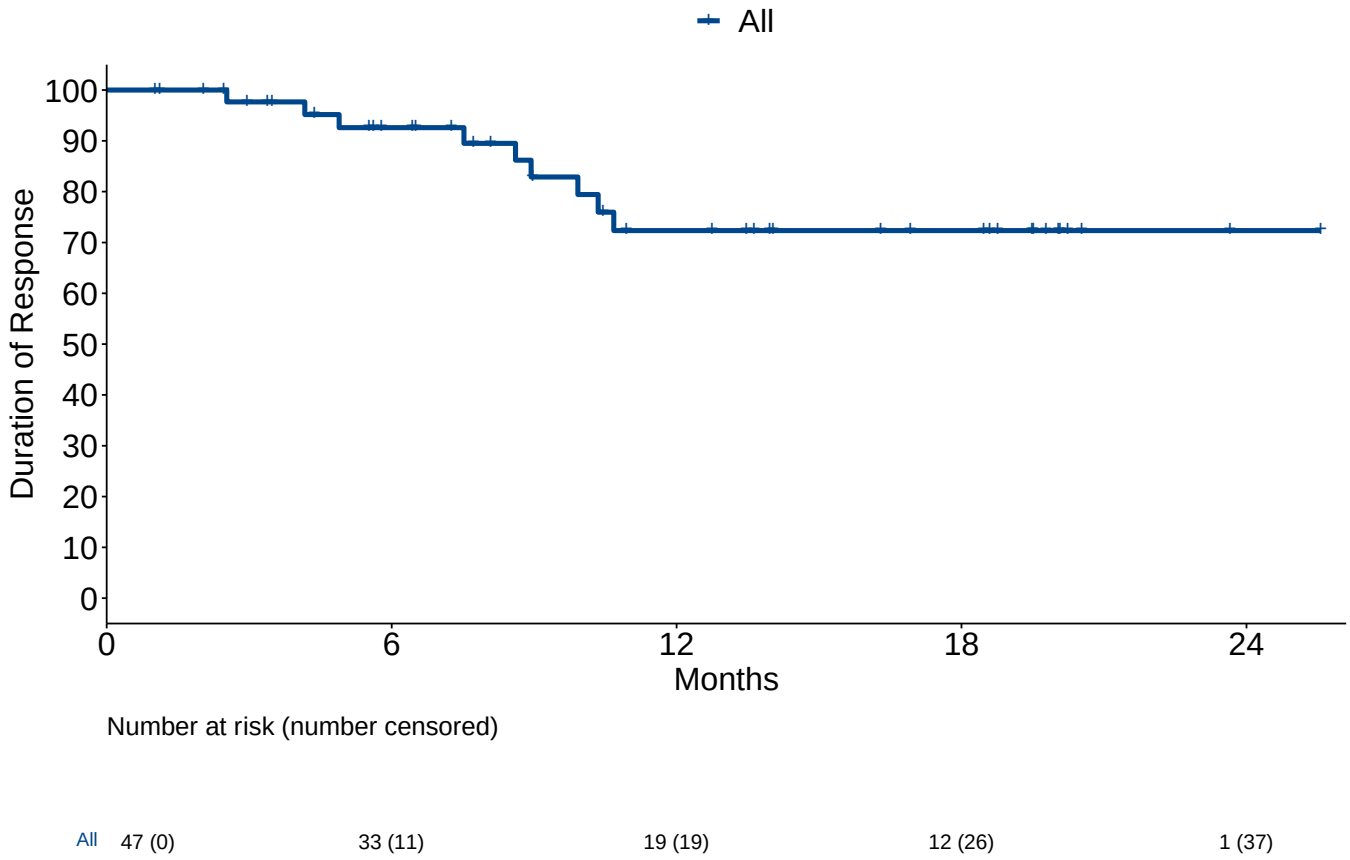


Figure S4: Overall survival Kaplan-Meier curve with censoring at time of allogenic stem cell transplant.

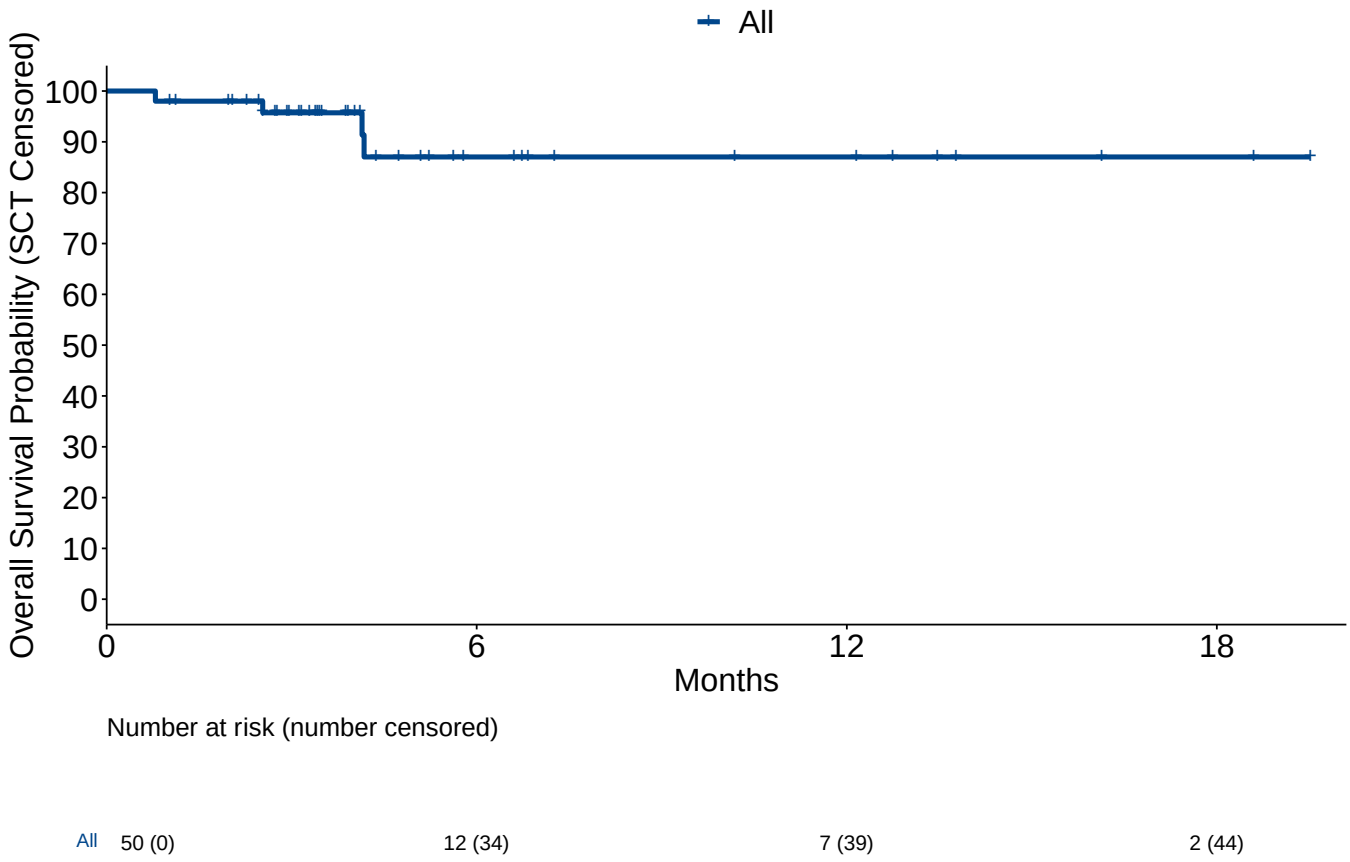
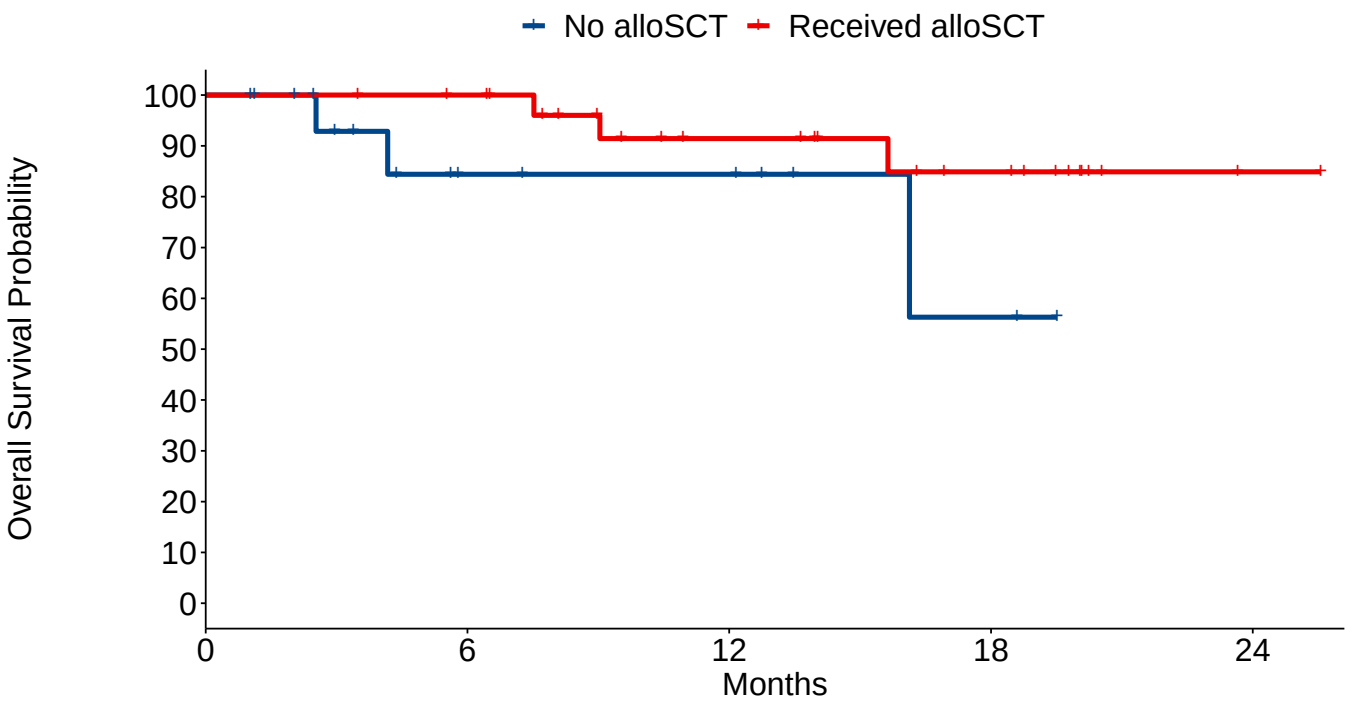


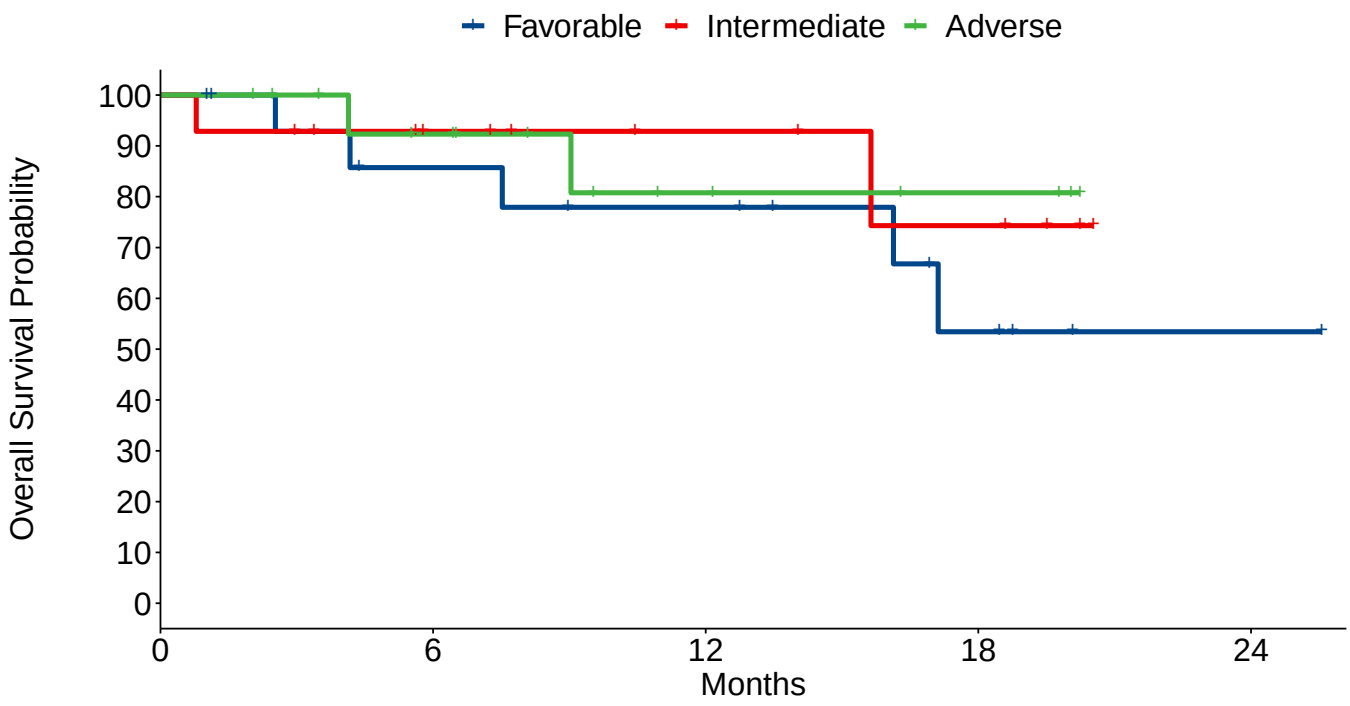
Figure S5: Overall survival Kaplan-Meier curve of responding patients by receipt of alloSCT



Number at risk (number censored)

No alloSCT	18 (0)	7 (9)	6 (10)	2 (13)	0 (15)
Received alloSCT	29 (0)	27 (2)	17 (10)	11 (15)	1 (25)

Figure S6: Overall survival Kaplan-Meier curve of AML patients stratified by ELN risk.



Number at risk (number censored)

Favorable	16 (0)	11 (3)	9 (4)	4 (7)	1 (10)
Intermediate	14 (0)	9 (4)	6 (7)	4 (8)	0 (12)
Adverse	16 (0)	11 (4)	5 (9)	3 (11)	0 (14)

Figure S7: A: OS of patients separated by treatment with a concomitant FLT3i. B: EFS of patients separated by treatment with a concomitant FLT3i.

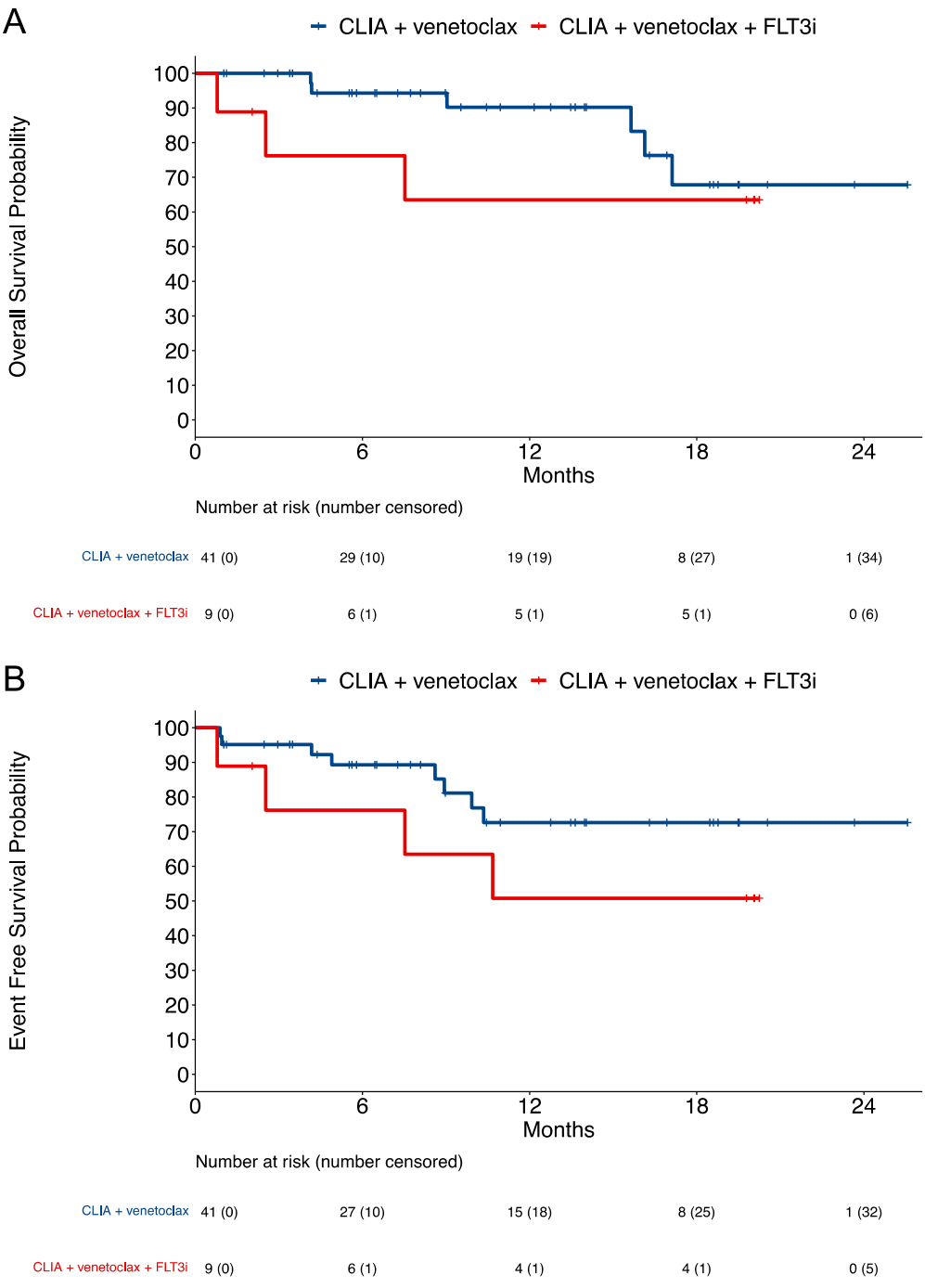
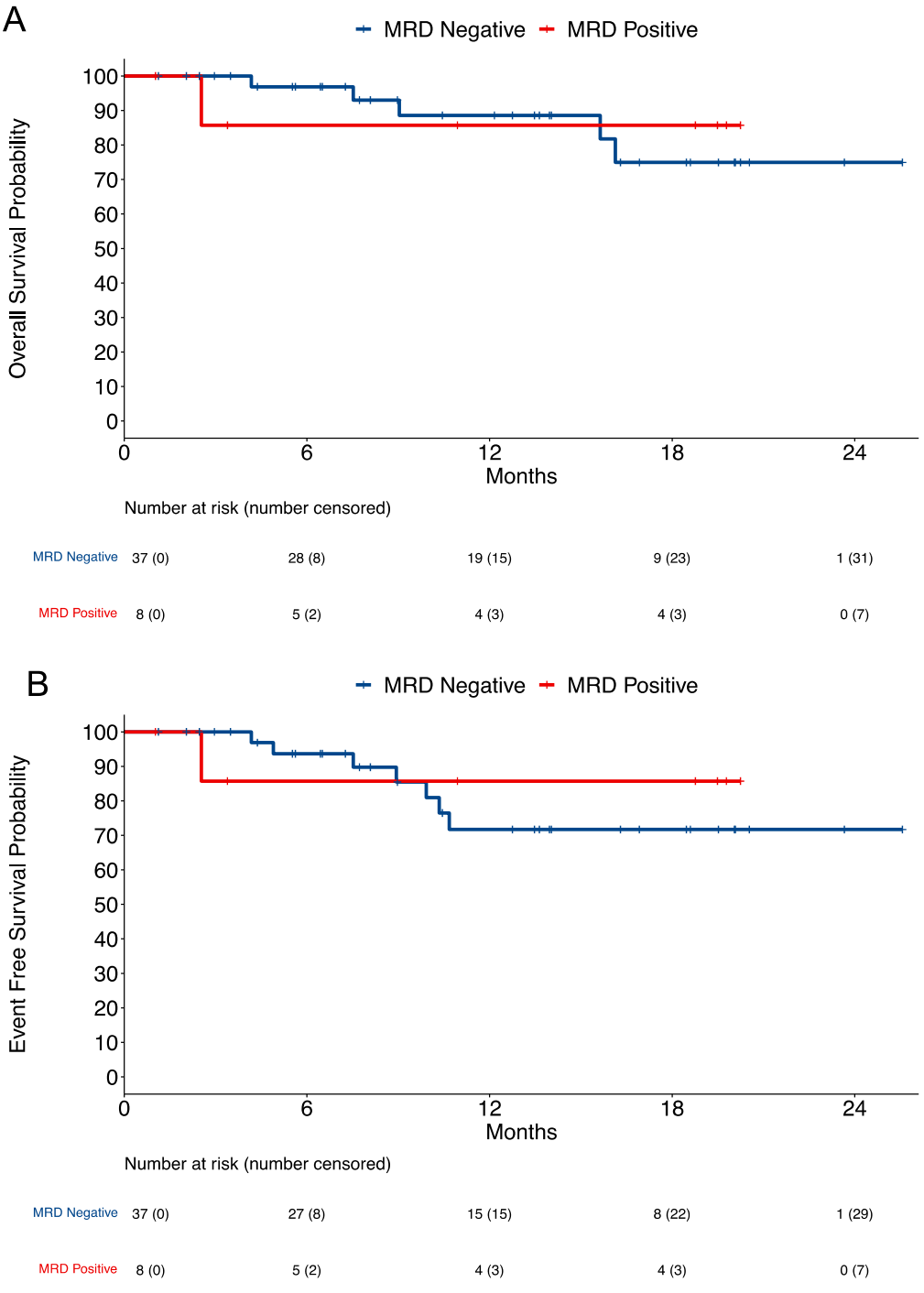


Figure S8: A: OS of responding patients by achievement of an MRD status. B: EFS of responding patients by achievement of an MRD status.



Full Inclusion/Exclusion criteria:

Inclusion Criteria:

1. Patients with a diagnosis of AML, Acute Biphenotypic Leukemia, or high risk MDS (>/= 10% blasts or IPSS >/= intermediate-2) will be eligible. Patients with CML in Myeloid Blast Phase are also eligible.
2. No prior potentially curative therapy for leukemia. Prior therapy with hydroxyurea, hematopoietic growth factors, azacytidine, decitabine, ATRA, or a total dose of cytarabine up to 2g (for emergency use for stabilization) is allowed. Patients deemed able to receive venetoclax (i.e. insurance clearance) will be assigned to Frontline cohort 4. Patients with secondary AML who have been treated for their antecedent myeloid neoplasm will be enrolled into the separate secondary AML cohort.
3. Age </= 65 years.
4. Adequate organ function as defined below:
    - liver function (bilirubin < 2mg/dL, AST and/or ALT <3 x ULN – or <5 x ULN if related to leukemic involvement)
    - kidney function (creatinine ≤ 1.5 x ULN).
    - known cardiac ejection fraction of > or = 45% within the past 6 months
5. ECOG performance status of ≤ 2.
6. A negative urine pregnancy test is required within 1 week for all women of childbearing potential prior to enrolling on this trial.
7. Patient must have the ability to understand the requirements of the study and signed informed consent. A signed informed consent by the patient or his legally authorized representative is required prior to their enrollment on the protocol.

Exclusion Criteria:

1. Pregnant women are excluded from this study because the agents used in this study have the potential for teratogenic or abortifacient effects. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with the chemotherapy agents, breastfeeding should also be avoided.
2. Uncontrolled intercurrent illness including, but not limited to active uncontrolled infection, symptomatic congestive heart failure (NYHA Class III or IV), unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
3. Patient with documented hypersensitivity to any of the components of the chemotherapy program.
4. Men and women of childbearing potential who do not practice contraception. Women of childbearing potential and men must agree to use contraception prior to study entry and for the duration of study participation.

Protocol:

PHASE II STUDY OF CLADRIBINE PLUS IDARUBICIN PLUS CYTARABINE (ARAC) IN PATIENTS WITH AML, HR MDS, OR MYELOID BLAST PHASE OF CML

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Study Product:	*Cladribine*
Protocol Number:	*2012-0648*
Coordinating Center:	*MD Anderson Cancer Center* *1515 Holcombe Blvd.* *Houston, TX 77030*

PHASE II STUDY OF CLADRIBINE, IDARUBICIN, AND ARAC IN PATIENTS WITH AML, HR MDS, OR MYELOID BLAST PHASE OF CML

1.0 OBJECTIVES

1.1 Primary objective

- To determine the complete response rate (CR) of cladribine in combination with idarubicin and araC in patients with AML, High risk (HR) MDS, or myeloid blast phase of CML.

1.2 Secondary objectives

- To determine the overall response rate (ORR) of cladribine in combination with idarubicin and araC in patients with AML, HR MDS, or myeloid blast phase of CML.
- To assess overall survival (OS) and event free survival (EFS) of patients treated with cladribine, idarubicin, and araC.
- To assess the duration of response to the combination in patients with AML, HR MDS, or myeloid blast phase of CML.
- To determine the safety and tolerability of the combination in patients with AML, HR MDS, or myeloid blast phase of CML.

1.3 Exploratory objectives

- To study and describe the relationship between pretreatment patient / disease characteristics (including AML-associated molecular abnormalities) and outcome
- To identify molecular biomarkers predictive of response to therapy.
- To study and describe the relationship between patient / disease characteristics, use of intrathecal prophylaxis, and incidence of leptomeningeal disease.
- To study the trajectories of leukemia mutations and molecular minimal residual disease (MRD) during the therapy.

2.0 BACKGROUND

2.1 Acute Myeloid Leukemia (AML)

AML is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 10,000 new cases per year. Age-adjusted incidence ranges from 1 per 100,000 in people < 20 years to > 10 per 100,000 in the elderly. AML represents approximately 90% of all acute leukemias in adults, and accounts for about 25% of all cases of leukemia diagnosed in the Western hemisphere.[1, 2] AML is a clonal myelopoietic stem cell disorder characterized by the accumulation of neoplastic cells in the bone marrow and in the peripheral circulation. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce complete remissions in about 55% - 60% of patients. Standard consolidation therapy with high doses of cytarabine leads to some improved survival in younger patients, but up to 70% of patients can be expected to relapse, so that only about 20-30% attain long-term disease-free survival.

A number of risk factors have been identified that predict the length of remission and the

possibility of long-term survival, including age, cytogenetics, and presence of minimal residual disease. Using a standard induction combination such as the 3+7 regimen (cytarabine plus an anthracycline), complete remission rates decrease by about 10% per additional decade of life, induction mortality can be substantial easily exceeding 20%, and remission durations are usually transient and rarely last more than 12 months. In higher risk patients, the median time from treatment to death is 5 to 10 months and less than 10% of patients stay in remission at 3 years.[3] Realizing the poor response with standard therapy, new agents and newer strategies are continuously being studied. The development of new and effective anti-AML approaches therefore remains a cornerstone of the continued efforts to improve the outcome of poor prognosis patients.[7] Combinations of araC with selected nucleoside analogues have shown significant synergy preclinically and have translated into improved clinical outcomes. Based on emerging data, double-nucleoside analogue based therapies may soon represent an important change in the standard of care of AML patients. Both cladribine and cytarabine have been studied in myeloid disorders, have single-agent AML activity, and are the main ingredients of the proposed study.

2.2 Cladribine in AML

Cladribine (2-chloro-2'-deoxyadenosine, 2-CDA) is a synthetic purine nucleoside analogue that is currently FDA approved for the treatment of symptomatic Hairy Cell leukemia.[8] Based on the success of cytarabine (AraC) in leukemia, 2-CDA was rationally designed to be resistant to degradation by adenosine deaminase and thereby increase its cytotoxicity. Cladribine's cytotoxic effects have been attributed to its ability to interfere with DNA synthesis in replicating cells[9] as well as inhibition of DNA repair and accumulation of DNA strand breaks in nonproliferating cells[10, 11]. Clinically, 2-CDA has been shown to have single-agent activity in hairy cell leukemia, chronic lymphocytic leukemia, as well as acute myeloid leukemia.[12, 13] Building on a phase I study in pediatrics[14] that confirmed safety and potential efficacy, Santana et. al.[15] conducted a phase II study of 2-CDA in pediatric patients with relapsed AML and ALL. Patients were given 2-CDA as a 5-day continuous infusion at a dose of 8.9 mg/m^2/d. Of 17 patients with AML, 8 (47%) achieved a CR and 2 (12%) achieved a PR, for an overall response rate of 59%. The drug was very well tolerated with the major toxicity being severe myelosuppression.

These initial promising results in pediatric AML led to followup studies in adults. In a phase I study of adults with relapsed or refractory AML, patients were given 2-CDA at doses ranging from 5 to 13 mg/m^2/d by continuous infusion for 7 days.[16] Of the 27 patients treated, 2 died before they could be evaluated and 16/25 remaining patients cleared their bone marrow of leukemia with regrowth in 9 patients after a median of 2 weeks. There were no complete remissions in this population. Toxicity was mild except for 3 cases of grade III or IV renal dysfunction. The MTD was defined as 10.8 mg/m^2/d x 7 days. The authors concluded that 2-CDA was a potent cytoreductive agent in adult AML, but not sufficient as a single-agent to yield CRs in this relapsed population. The importance of this study is that it served as a lead-in to a combination trial with AraC[16, 17] that utilized intracellular pharmacodynamic data and was based on preclinical models of synergy between the 2 compounds.[18]

The cytotoxicity and clinical activity of AraC, the most active agent in AML, is directly related to the intracellular generation and retention of ara-CTP (the triphosphate form). Strategies that increase intracellular ara-CTP are therefore desired to increase its activity. 2-CDA is a potent inhibitor of ribonucleotide reductase and therefore leads to a significant decrease in intracellular deoxynucleotide pools. This has 2 major effects with respect to intracellular AraC. First, it augments the activity of deoxycytidine kinase which rapidly generates intracellular ara-CTP from araC. Second, as a result of the depletion of normal intracellular deoxynucleotides, ara-CTP and Cd-ATP (the triphosphate form of 2-CDA) become more prominent as substrates for DNA polymerase in dividing cells. They are more likely to get incorporated into DNA and exert their cytotoxic effects. This hypothesis has been confirmed in preclinical studies. In vitro incubation of AML blasts with 2-CDA followed by araC produced a higher rate of ara-CTP accumulation than araC alone.[19]

As an extension of the aforementioned phase I study of 2-CDA in adults with AML, a phase II study combining araC 1 g/m^2 with 2-CDA 12mg/m^2/d x 5 days was conducted to test this hypothesis clinically.[16, 17] Of the 17 patients treated, 2 patients achieved a CR (12%) and 69% cleared their bone marrow. Correlative studies from this trial confirmed a median 40% increase in the rate of ara-CTP accumulation in the leukemia blasts of patients after pretreatment with 2-CDA. In addition, the DNA synthetic capacity of the circulating blasts was inhibited to a greater extent by administration of 2-CDA and ara-C in combination than by either one alone. Both 2-CDA and ara-C (CdAMP and ara-CMP, respectively) were found to be incorporated into DNA, with the tandem incorporation having the most potent chain-termination effect.[17] This strategy of combining a potent ribonucleotide reductase inhibitor with araC to increase its clinical activity has been successfully replicated using other nucleoside analogues such as fludarabine[20-22] and clofarabine.[23]

Based on this data, several groups have studied combinations of 2-CDA and different doses of AraC in the treatment of AML. In a multicenter phase II study[24] from the Polish Adult Leukmia Group (PALG) 58 patients with refractory AML (50 primarily resistant and 8 with short CR durations) were treated with 2-CDA (5 mg/m^2/d IV over 2 hrs x 5 days) combined with ara-C (2 g/m^2/d IV over 4 hrs - starting 2 hrs after CDA x 5 days) and G-CSF (300 µg subcutaneously daily x 6 days). The CR rate was 50%. Notably 5/6 (83%) of patients with MDS/AML achieved a remission. Myelosuppression was the most prominent toxicity. The 1-yr overall survival for the entire cohort and for those who achieved a CR was 42% and 65%, respectively and the disease free survival (DFS) at 1 year was 29%.

Investigators from Sweden conducted a randomized phase II trial[25] in de novo AML patients aged > 60 years, comparing the combination of 2-CDA + ara-C + idarubicin (CCI) to ara-C + idarubicin (CI). A total of 63 patients with a median age of 70 years were randomized 2:1 to treatment with 2-CDA (5 mg/m^2/d IV over 1 hr x 4 days) plus ara-C (1 g/m^2/d IV over 2 hrs x 4 days) plus idarubicin (10 mg/m^2/d IV over 1 hr x 2 days) versus the 2 drug combination. The CR rate was 51% for CCI vs 35% for CI (p=0.014). There were no differences in toxicity between the 2 arms. The median

overall survival was 14 months, with a 2-year survival over 30%. There was no significant difference in survival between the 2 arms.

The PALG conducted a similar study combining 2-CDA, an anthracycline, and a lower dose of araC in younger patients with untreated AML. Among 50 patients treated with 2-CDA (5 mg/m^2/d IV over 1 hr x 5 days) plus ara-C (200 mg/m^2/d IV x 7 days) plus daunorubicin (60 mg/m^2/d IV daily x 3 days), the CR rate was 72%. This led to the phase III multicenter study[26] comparing this combination (DAC-7) with daunorubicin and ara-C without cladribine. A total of 400 patients with a median age of 45 were randomized to the daunorubicin plus cytarabine (DA-7) or the 3-drug combination outlined above (DAC-7). The CR rate after a single course of therapy was 64% for DAC-7 vs. 47% for DA-7 (p=0.0009). The median hospitalization time was shorter for DAC-7 vs. DA-7 (33 vs. 40 day, p=0.002). Toxicity was comparable between both groups and primarily consisted of myelosuppression and its sequelae. Overall, the probability of leukemia free survival (LFS) was 43% and 34% between DAC-7 and DA-7, respectively (p=NS). However, in patients aged > 40 years, there was a trend for higher LFS in those who received DAC-7 (44% vs. 28%, p=0.05). These studies demonstrate tolerability and suggest enhanced antileukemia efficacy with the addition of cladribine to induction regimens.

We recently implemented our own study using cladribine and lower dose araC in older patients with AML. Our preliminary results submitted to the American Society of Hematology meeting (Kadia, et. al. ASH 2013) confirmed the efficacy of cladribine in this disease: among 45 pts enrolled thus far with a median age of 69, the ORR was 67%, with a CR rate of 58%. With a median followup of 3.2 months, the median CR duration was not reached and the 1-year OS estimate was 51%. Based on these encouraging results in older patients, we aim to incorporate cladribine into our intensive induction program for younger, fit patients.

2.3 Anthracyclines in AML

Anthracyclines have traditionally been an important component of standard induction regimens for AML. The current standard (which exploits their synergy) involves the combination of an anthracycline such as idarubicin or daunorubicin for 3 days with standard-dose araC for 7 days, often referred to as the "3+7" regimen. Two recent publications reporting the improved efficacy higher doses of daunorubicin highlight the activity of this class of agents in therapy of AML. In a French study, Pautas, et. al. studied the efficacy of idarubicin compared to daunorubicin in AML. In a 3-arm study, 468 patients were randomized to idarubicin 12 mg/m2/d x 3 days, idarubicin 12mg/m2/d x 4 days, or (high-dose) daunorubicin 80 mg/m2/d x 3 days. The CR rate with idarubicin x 3 days was higher than that of high-dose daunorubicin (83% vs. 70%), as was the 3-year event free survival rate (23% vs. 16%). Our current standard induction therapy at MD Anderson is therefore idarubicin 12 mg/m2/d x 3 days plus araC 1.5 grams/m2/d x 4 days.

2.4 Rationale for studying cladribine, ara-C, and idarubicin in patients with AML

In the current study, we aim to add cladribine to our standard induction therapy of idarubicin and araC in patients with acute myeloid leukemia. The 3-drug combination aims to exploit both the single-agent activity of each of the component drugs, as well as their synergy. As described above, the addition of cladribine as a potent ribonucleotide reductase inhibitor works to increase intracellular ara-C concentrations and thereby improve its antileukemic efficacy. Our own experience with cladribine + araC in older AML (Kadia, et. al. ASH 2013) confirms this efficacy. The addition of idarubicin works synergistically with araC in AML. We have studied a similar 3 drug combination, with a similar rationale – using clofarabine, idarubicin, and araC (CIA) in patients AML. The doses used in this study were as follows: clofarabine 20 mg/m2/d x 5 days, idarubicin 10 mg/m2/d x 3 days, and araC 1 g/m2/d x 5 days. Our experience was recently published (Nazha et.al., Am Journ Hematol 2013), showing an ORR of 79% and EFS of 13.5 months. With a median followup of 10.9 months, the median OS was not reached. Based on our own experience with the lower intensity cladribine +araC combination, cladribine has a different safety profile compared to clofarabine and may be better tolerated. Additionally, investigators from Poland (using lower doses of araC) and Sweden (using similar doses of araC) have showed that this same 3-drug combination of cladribine, idarubicin, and araC is both safe and more effective than the 2-drug backbone (without cladribine). However, unlike the Swedish study which used similar doses of araC to our study, we are treating a younger population – where the response rates are expected to be higher and the intense regimen better tolerated.

This study has been designed to study the efficacy and safety of this combination in our own, younger patients with AML, higher risk MDS, as well as those with myeloid blast phase CML. This will extend our experience with double-nucleoside analogue combinations in AML, adding to our previous experience with fludarabine/araC and clofarabine/araC – and eventually setting up a comparison among them. The 3-drug regimen will be offered to both frontline patients, as well as those requiring salvage therapy for relapsed or refractory disease. In addition to relapsed and refractory patients, we recognize an additional subset of patients that we commonly see in in clinic and have a poor overall outcome: those with secondary acute myeloid leukemia (AML) arising from a previous myeloid neoplasm such as myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or aplastic anemia (AA). These are patients that have received prior therapies for their myeloid disorder (often for months to years) prior to transforming to AML. When they come for AML treatment, they are technically considered 'frontline' AML, but have often been heavily pretreated for their preceding myeloid neoplasm. The response rates and outcomes of these patients with secondary AML are clearly inferior to *de novo* frontline AML. We recently analyzed our own experience with patients with secondary AML who are receiving their initial AML therapy at MD Anderson Cancer Center. We evaluated the cases of 996 patients with secondary AML treated in our department from 2012 – 2015. One hundred thirty-five patients had received one or two therapies for their antecedent myeloid disorder prior to being diagnosed with AML. Among these patients the rate of CR/CRp was 22%-28%, reflecting the challenging nature of this population and reinforcing the need for more active therapies. It is clear, therefore, that the expected response rates for this cohort of newly-diagnosed secondary AML is discordant from *de novo* AML. For this reason, we

are allowing a separate cohort of patients to be analyzed separately within the protocol. The protocol will therefore have 3 cohorts: (1) those with de novo, untreated AML, (2) those with secondary, untreated AML, and (3) those with relapsed/refractory AML. Each cohort will be analyzed separately with regards to efficacy and safety.

Addition of small molecule inhibitors of aberrantly activated tyrosine kinase inhibitors to chemotherapy have led to improved outcomes. As per our current departmental practice in leukemia, appropriate targeted small-molecule inhibitors will be offered to patients with targetable activating mutations found on initial screening. Specifically, those with FLT3 mutations will be offered sorafenib in conjunction with the chemotherapy. Those patients with the presence of the Philadelphia chromosome or bcr-abl rearrangement will be offered a commercially available tyrosine kinase inhibitor (TKI) in conjunction with chemotherapy.

We presented interim results from this trial at the American Society of Hematology (ASH) meeting in December 2016. A total of 117 patients were evaluable: 53 patients in the frontline cohort, 51 patients in the relapsed/refractory (R/R) cohort, and 13 patients in the secondary AML cohort. The treatment regimen was composed of the following doses: idarubicin 10 mg/m2/d x 3 days and araC 1 g/m2/d x 5 days combined with cladribine 5 mg/m2/day for 5 days. The overall response rates for each cohort were as follows – frontline: 83% (CR=77%), R/R: 39% (CR=22%), and secondary: 46% (CR=23%). The 4-week induction mortality rates were 0%, 6%, and 1%, respectively. The median OS survival for each cohort was not reached, 8.8 months, and 4.8 months, respectively. The 1-year OS estimates for each of the subgroups were 75%, 40%, and 0%, respectively. While these results exceed our pretreatment expectations for response and tolerability, we aim to improve on this backbone to continue and improve long term outcomes.

Recent data has shown the benefit of higher doses of cytarabine as part of induction and consolidation strategies. The UK-MRC AML group demonstrated the benefit of the FLAG-Ida regimen, including fludarabine, idarubicin, and higher dose cytarabine in patients with newly diagnosed AML. This was particularly evident in younger patients. Since we have developed a robust level of comfort and experience with current regimen and have confirmed the safety and efficacy, we aimed to investigate higher doses of cytarabine for subsequent enrollment on the trial.

In addition to continuous monitoring for safety and efficacy, we performed an ad hoc interim analysis to review the efficacy of this approach in our frontline cohort. Among 35 evaluable patients with a median age of 46 years, the rate of CR + CRi was 89%, with a 4-week mortality rate of 0% and an 8-week mortality of 3%. In the R/R (N=14) and secondary cohorts (N=10), the ORR were 57% and 60%, respectively with similar rates of early mortality. These results compare favorably to our prior approach with lower dose CLIA and to our prior experience with doublet chemotherapy regimens. With the advent of newer targeted approaches and recognition of new molecular subsets, we aim to expand our experience with this backbone regimen and demonstrate longer term data. This will allow us to (1) establish this regimen as a potential new standard of care – to be eventually tested in randomized trials, and (2) allow us to interrogate larger cohorts of

molecular subsets to understand differential responses and resistance.

2.5 BCL-2 Inhibitors in AML

Hematologic malignancies, including leukemias are highly dependent upon the anti-apoptotic protein BCL-2 for survival. Over-expression of BCL-2 is associated with tumor initiation, disease progression, and drug resistance, and is thus a compelling target for anti-tumor therapy. Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity for BCL-2 (K_i < 0.010 nM) than for BCL-X_L (Ki = 48 nm) or MCL-1 (K_i > 444 nM).[13] In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines, including acute myeloid leukemia (AML). Venetoclax was especially potent against non-Hodgkin's lymphoma (NHL) cell lines expressing high levels of BCL-2 protein due to the t(14;18) chromosome translocation, amplification of the *BCL-2* gene locus, or aberrantly activated signaling mechanisms.

BCL-2 over-expression has also been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. In addition, high levels of BCL-2 were associated with poor survival in a subset of patients with this disease.[2,3] The BCL-2/BCL-X_L inhibitor ABT-737 has been shown to kill AML cells, including leukemic stem/progenitor cells, as both a single agent and in combination with cytarabine[2] or 5-azacitidine.[14] To further define the role of BCL-2 in this disease, panels of AML cell lines and primary patient samples were cultured in the presence of venetoclax. Twelve of 24 AML cell lines tested were sensitive to venetoclax, with cell killing IC_{50} values of < 1.0 μM. The sensitivity of primary AML subject samples was comparable to that observed for primary CLL samples, with a median IC_{50} = 0.010 μM (n = 57) for AML versus a median IC_{50} = 0.003 μM (n = 35) for CLL (AbbVie R&D/10/1025, AbbVie R&D/12/538). Venetoclax has also demonstrated killing of AML leukemic stem/progenitor cells ex vivo and antitumor efficacy in vivo, inhibiting the growth of AML cell lines or AML patient-derived primary cells systemically engrafted into immunocompromised mice. Single agent venetoclax has been studied in relapsed/refractory (R/R) AML and was found to induce rapid reduction in blast counts in some patients indicating activity in subject with this disease.[15] Patients were treated at a dose of 800mg daily, with the option to escalate to 1200 mg daily in those with suboptimal response. Tumor lysis syndrome (TLS) was not seen and the drug was well tolerated, with myelosuppression being the most notable toxicity. Among 32 patients, the overall response rate was 19% (6/32) with 6% of patients achieving a complete response (CR) and 13% achieving a CR with incomplete count recovery (CRi). Notably, 3 of the 6 responding patients had a history of an antecedent hematologic disorder and 4 of the 6 patients had mutations in the isocitrate dehydrogenase (IDH1 or IDH2) gene. Promising single-agent activity has led to further investigation into combinations with chemotherapy in AML.

Two important studies have demonstrated the activity venetoclax in combination with low intensity chemotherapy in newly diagnosed AML and have led to its accelerated approval. A phase Ib investigated the combination of venetoclax with HMAs (decitabine

[DAC] or azacytidine [AZA]) in newly diagnosed, older patients with AML. Among 145 patients with a median age of 74 years, 49% of whom had adverse karyotype, the overall response rate (CR+CRi+PR)) was 68%.[12] The responses were brisk, with a median 1.2 months to achieving first response and median of 2.1 to achieving best response. The median CR duration was 11.3 months and a median OS of 17.5 months for all patients (Dinardo, et al. Blood 2018). The combination was well tolerated and the 400 mg of venetoclax was the recommended phase II dose. In a recent update at the ASH meeting in December 2018, Pollyea, et al reported updated results of patients in the study receiving 400mg of venetoclax combined with HMA. Among patients receiving either 5-azacytidine or decitabine, the CR/CRi rates were 71% and 74%, respectively, with a median CR duration of 21.2 months and 15 months, respectively. The median OS in each group was 16.9 and 16.2 months, respectively.

A second study investigated the combination of low-dose araC (LDAC) given at a dose of 20 mg/m^2 SQ on D1-10 with venetoclax 600 mg PO daily on D1-28 of a 28 day cycle in older patients with newly diagnosed. The median age of patients on this study was 74 years, with 49% of patients having history of an antecedent hematologic disorder. The overall response rate (CR, CRi, PR) was 54% with a median CR duration of 8.1 months and a median OS of 10.1 months in all patients. 33% patients with exposure to prior HMA-based therapy achieved a response. The combination was well tolerated in this older population with no clinical TLS and the most common serious adverse events being febrile neutropenia (42%) and thrombocytopenia (38%) (Wei, et al. ASH 2018).

Finally, there is an ongoing study of venetoclax in combination with the high dose cytarabine-based FLAG + idarubicin regimen in patients with newly diagnosed patients. Venetoclax was given for 14-21 days. Preliminary data from a lead-in safety phase in patients with R/R AML demonstrate that combining venetoclax with more intensive chemotherapy is safe and feasible (Dinardo, Albitar, Kadia, et al. ASH 2018). Among patients with R/R AML with a median age of 46 years, the CR/CRi rate was 73%. The 4- and 8-week mortality was 0%. The most common grade ≥ 3 adverse events included neutropenic fever and infection. No significant tumor lysis syndrome was observed; 40% of patients who were treated were able to go on to allogeneic stem cell transplant, including 55% of pts who had achieved a response.

In November 2018, venetoclax received accelerated FDA approval in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML). In view of this new approval, we will allow the addition of venetoclax to current CLIA regimen with the goal to further improve outcomes. In an effort to study the safety and efficacy of this approach, a 4th cohort has been created for untreated patients treated with CLIA and the addition of venetoclax.

2.6 Cladribine

Cladribine is available commercially. Please refer to the package insert for full details.

Cladribine Injection (also commonly known as 2-chloro-2´-deoxy-ß-D-adenosine) is a synthetic antineoplastic agent for intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. Cladribine Injection is available in single-use vials containing 10 mg (1 mg/mL) of Cladribine, a chlorinated purine nucleoside analog. Each mL of Cladribine injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3 ± 0.3.

The selective toxicity of 2-chloro-2´-deoxy-ß-D-adenosine towards certain normal and malignant leukocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2´-deoxy-ß-D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2´-deoxy-ß-D-adenosine is resistant to deamination by adenosine deaminase, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2´-deoxy-ß-D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2´-deoxy-ß-D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2´-deoxy-ß-D-adenosine is cytotoxic to both actively dividing and quiescent cells, inhibiting both DNA synthesis and repair.

Cladribine plasma concentration after intravenous administration declines multi-exponentially with an average half-life of 6.7 + 2.5 hours. In general, the apparent volume of distribution of Cladribine is approximately 9 L/kg, indicating an extensive distribution in body tissues.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

Cladribine is bound approximately 20% to plasma proteins.

2.7 Cytarabine

Cytarabine is available commercially. Please refer to the package insert for full details.

Cytarabine is a deoxycytidine analog that is metabolized to cytarabine triphosphate, a substance that inhibits DNA polymerase. It is S phase specific, and thus affects DNA synthesis. It has an initial plasma half-life of about 15 minutes, with a secondary phase of about 2 hours, and is rapidly catabolized by hepatic cytidine deaminases to Ara-U.

Cytarabine injection, an antineoplastic is a sterile solution of cytarabine for intravenous administration. Each mL contains 20 mg cytarabine in 100 mg (20 mg/mL) single dose vials and 100 mg cytarabine in 2 g (100 mg/mL) single dose vial.

Cytarabine injection 100 mg/5 mL is a sterile solution for intravenous administration. Each mL contains 20 mg cytarabine USP, and the following inactive ingredients: sodium chloride 6.8 mg and Water for Injections qs. When necessary the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a pH of 7.7.

Chemical stability studies were performed by ultraviolet assay on cytarabine injection in infusion solutions. These studies showed that when cytarabine injection was added to Water for Injection, 5% Dextrose in Water or Sodium Chloride Injection, 94% to 96% of the cytarabine was present after 192 hours storage at room temperature. Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

2.8 Idarubicin

Idarubicin is available commercially. Please refer to the package insert for full details.

Idarubicin HCl Injection contains idarubicin hydrochloride and is a sterile, semi-synthetic, preservative-free solution antineoplastic anthracycline for intravenous use. Chemically, idarubicin hydrochloride is (1S,3S)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-6,11- dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy-_-L-lyxo-hexopyranoside, hydrochloride.

Idarubicin HCl Injection is a sterile, red-orange, isotonic parenteral preservative-free solution, available in 5 mL (5 mg), 10 mL (10 mg) and 20 mL (20 mg) single-use-only vials. Each mL contains idarubicin HCI 1 mg and the following inactive ingredients: glycerin 25 mg and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of 3.5.

Idarubicin is intended for administration under the supervision of a physician who is experienced in leukemia chemotherapy. Idarubicin is a potent bone marrow suppressant. Idarubicin should not be given to patients with pre-existing bone marrow suppression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk.

Severe myelosuppression will occur in all patients given a therapeutic dose of this agent for induction, consolidation or maintenance. Careful hematologic monitoring is required. Deaths due to infection and/or bleeding have been reported during the period of severe myelosuppression. Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain a patient compromised by drug toxicity should be available. It must be possible to treat rapidly and completely a severe hemorrhagic condition and/or a severe infection.

Pre-existing heart disease and previous therapy with anthracyclines at high cumulative doses or other potentially cardiotoxic agents are co-factors for increased risk of

idarubicin-induced cardiac toxicity and the benefit to risk ratio of idarubicin therapy in such patients should be weighed before starting treatment with idarubicin.
Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias or other cardiomyopathies may occur following therapy with idarubicin. Appropriate therapeutic measures for the management of congestive heart failure and/or arrhythmias are indicated.

Cardiac function should be carefully monitored during treatment in order to minimize the risk of cardiac toxicity of the type described for other anthracycline compounds. The risk of such myocardial toxicity may be higher following concomitant or previous radiation to the mediastinal-pericardial area or in patients with anemia, bone marrow depression, infections, leukemic pericarditis and/or myocarditis. While there are no reliable means for predicting congestive heart failure, cardiomyopathy induced by anthracyclines is usually associated with a decrease of the left ventricular ejection fraction (LVEF) from pretreatment baseline values. Since hepatic and/or renal function impairment can affect the disposition of idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to and during treatment. In a number of Phase III clinical trials, treatment was not given if bilirubin and/or creatinine serum levels exceeded 2 mg%. However, in one Phase III trial, patients with bilirubin levels between 2.6 and 5 mg% received the anthracycline with a 50% reduction in dose. Dose reduction of idarubicin should be considered if the bilirubin and/or creatinine levels are above the normal range.

2.9 Venetoclax

Venetoclax is available commercially. Please refer to the package insert for full details.

Venetoclax (also referred to as ABT-199, A-1195425.0, GDC-0199, RO5537382, Venclexta®, and Venclyxto®) is a novel, orally bioavailable, small-molecule B-cell lymphoma-2 (Bcl-2) family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax binds with high affinity (inhibition constant [K_i] < 0.010 nM) to antiapoptotic protein Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like B-cell lymphoma–extra large (Bcl-X_L) and B-cell lymphoma- Walter and Eliza Hall Institute (Bcl-w) (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).

Venetoclax was first approved in the United States (US) on 11 April 2016 through accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) with deletion of the p13 locus on chromosome 17 (17p del) (as detected by a Food and Drug Administration [FDA]-approved test) who have received at least 1 prior therapy, as described in the US Package Insert (USPI). Subsequently, venetoclax was also approved in Argentina on 29 August 2016 and in Canada on 30 September 2016. Market applications for the use of single agent venetoclax in relapsed or refractory (R/R) CLL patients were also submitted and are currently under review with various health authorities, including the European Medicines Agency. On 21 November 2018, venetoclax received accelerated FDA approval in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid

leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Nonclinical Experience

Oncology Nonclinical Pharmacology: In vitro, venetoclax demonstrated cell killing activity against patient-derived CLL and acute myeloid leukemia (AML) cells and a variety of lymphoma and leukemia cell lines, including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B-cell lymphomas (DLBCLs), AMLs, and multiple myeloma (MM) cell lines. Venetoclax was especially potent against non-Hodgkin lymphoma (NHL) cell lines expressing high levels of Bcl-2. Venetoclax inhibits subcutaneous xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL), NHL, and AML, and is highly efficacious using various doses and combined with other regimens. The drug is also active in a model of disseminated ALL and AML. Venetoclax enhanced the activity of a broad variety of chemotherapeutic agents in other human hematological models. Specifically, venetoclax enhances the efficacy of bendamustine plus rituximab (BR) in models of MCL and DLBCL. Furthermore, venetoclax demonstrated potential to enhance the efficacy of bortezomib in multiple models of MM.

Clinical Experience

Clinical Pharmacokinetics: Pharmacokinetic data for venetoclax are available from studies in subjects with cancer (CLL/SLL, AML, NHL, and MM), healthy subjects, and a single study in subjects with SLE. Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained 5 to 8 hours after dosing. The harmonic mean terminal half-life ($t_{1/2}$) ranged from 17 to 41 hours following a single oral dose of venetoclax. In subjects with CLL, venetoclax showed minimal accumulation, and steady-state AUC increased proportionally over the dose range of 150 to 800 mg. Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with unbound fraction (f_u) < 0.01, and it is primarily eliminated as metabolites in feces with negligible renal elimination (< 0.1%).

Drug-drug interaction studies of venetoclax with ketoconazole, rifampin, warfarin, ritonavir, and digoxin were conducted to provide dosing recommendations for patients concomitantly taking CYP3A and/or P-gp inhibitors, inducers, and/or warfarin. Pharmacokinetic studies were conducted in healthy Chinese subjects and in Japanese subjects to provide dosing recommendations for those specific populations.

Additionally, a dedicated study to evaluate the pharmacokinetics of venetoclax in subjects with hepatic impairment is ongoing. Based on the population pharmacokinetic analysis, age, sex, race, weight, mild and moderate renal or hepatic impairment do not have an effect on venetoclax clearance.

Preliminary safety results in oncology subjects:
The overall safety of venetoclax is well described and largely consistent across all

indications. Important identified risks are TLS, particularly in CLL and mantle cell indications, and neutropenia. Serious infection is a potential risk. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including, anemia, thrombocytopenia, and lymphopenia); however anemia, neutropenia, and thrombocytopenia are commonly observed in hematologic malignances and this may provide alternative causality. Co-administration with CYP3A inducers and inhibitors can cause changes in venetoclax exposure requiring venetoclax dose adjustments. Decreased spermatogenesis has been observed in nonclinical studies with dogs. Embryofetal toxicity was observed in nonclinical studies; thus, venetoclax should not be used during pregnancy. In addition, as venetoclax is being evaluated in subjects with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria:

1. Patients with a diagnosis of AML, Acute Biphenotypic Leukemia, or high risk MDS (>/= 10% blasts or IPSS >/= intermediate-2) will be eligible. Patients with CML in Myeloid Blast Phase are also eligible.
2. **For Frontline cohort (1 or 4):** No prior potentially-curative therapy for leukemia. Prior therapy with hydroxyurea, hematopoietic growth factors, azacytidine, decitabine, ATRA, or a total dose of cytarabine up to 2g (for emergency use for stabilization) is allowed. Patients deemed able to receive venetoclax (ie. insurance clearance) will be assigned to Frontline cohort 4. Patients with secondary AMLwho have been treated for their antecedent myeloid neoplasm will be enrolled into the separate **Secondary AML cohort.**
3. **For Salvage cohort:** Patients with previously treated, relapsed or refractory AML, Acute Biphenotypic Leukemia, or CML in Myeloid Blast Phase are eligible.
4. Age </= 65 years.
5. Adequate organ function as defined below:
    - liver function (bilirubin $\leq$ 2mg/dL, AST and/or ALT $\leq$3 x ULN – or $\leq$5 x ULN if related to leukemic involvement)
    - kidney function (creatinine $\leq$ 1.5 x ULN).
    - known cardiac ejection fraction of > or = 45% within the past 6 months
6. ECOG performance status of $\leq$ 2.
7. A negative urine pregnancy test is required within 1 week for all women of childbearing potential prior to enrolling on this trial.
8. Patient must have the ability to understand the requirements of the study and signed informed consent. A signed informed consent by the patient or his legally authorized representative is required prior to their enrollment on the protocol.

3.2 Exclusion Criteria

1. Pregnant women are excluded from this study because the agents used in this

study have the potential for teratogenic or abortifacient effects. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with the chemotherapy agents, breastfeeding should also be avoided.

2. Uncontrolled intercurrent illness including, but not limited to active uncontrolled infection, symptomatic congestive heart failure (NYHA Class III or IV), unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
3. Patient with documented hypersensitivity to any of the components of the chemotherapy program.
4. Men and women of childbearing potential who do not practice contraception. Women of childbearing potential and men must agree to use contraception prior to study entry and for the duration of study participation.

4.0 TREATMENT PLAN

This is a phase II study investigating the efficacy and safety of the combination of cladribine, idarubicin, and araC in patients with AML. There are 4 cohorts of patients that will be treated and analyzed separately: (1) frontline, untreated AML/MDS, (2) relapsed or refractory AML requiring salvage chemotherapy, (3) those with secondary AML who have received treatment for their antecedent myeloid disorder (eg. myelodysplastic syndrome, myeloproliferative disorder, aplastic anemia, etc.), and (4) frontline, untreated AML/MDS treated with venetoclax added to CLIA backbone.

Cladribine, idarubicin and araC will be given at the doses outlined below. Missed doses can be made up if given within 7 days of the first dose, after discussion with PI. One cycle will be defined as 4 weeks. After the initial "induction" cycle, if the patient achieves a remission, he/she can then undergo up to 5 additional "consolidation" cycles per protocol. If the patient does not achieve a remission after the first induction, 1 additional induction cycle may be given at the same dose and schedule, followed by up to 4 additional consolidation cycles. If the patient does not achieve a response (CR, CRi, or PR) after the 2nd induction, the patient will be taken off the study unless there is evidence that the patient is deriving benefit from the treatment.

Treatment will be continued during the duration of the study unless patient exhibits evidence of clinically significant treatment failure, clinically significant disease progression, unacceptable toxicity, or if the investigator determines that discontinuation is in the best interest of the patient.

Patients will be treated with the study drugs per protocol, based on the calculation of the patient's body surface area (BSA). The BSA will be calculated at baseline using the patient's baseline height and weight. Chemotherapy doses will be recalculated only if there is a greater than 10% change in weight from baseline.

All induction and consolidation intravenous infusions will be administered at MD Anderson Cancer Center (MDACC).

The objective is to determine the efficacy of this combination in achieving CR, ORR (CR, CRp, CRi), and its effect on EFS and OS. All patients will be registered for the protocol via the Clinical Oncology Research (CORe) system at MDACC (single institution study).

4.1 Treatment Schema

INDUCTION:
Cladribine at a dose of 5 mg/m^2/day will be given IV over approximately 1 to 2 hours, daily on days 1-5 combined with cytarabine at the appropriate dose noted below IV over 2 hours daily on days 1-5. The cytarabine should be initiated approximately 3-6 hours following the start of the cladribine infusion. Idarubicin will given at a dose of 10 mg/m^2/day IV over 30-60 minutes on days 1-3.

Induction – Cytarabine dose		
Age	**Cytarabine dose (cohorts 1-3)**	**Cytarabine dose (cohort 4 – addition of Venetoclax)**
Age < 60 years	2 grams/m^2	1.5 grams/m^2
Age > or = 60 years	1.5 grams/m^2	1 gram/m^2

Due to inter-individual differences in age, performance status, and fitness for intensive chemotherapy, dose-reductions are commonly implemented during induction per the treating physician's judgment. Therefore, in patients with a **PS=2** or **age ≥ 60 years**, the number of days of cladribine and araC may be reduced to **4 days**, or **3 days** in the judgment of the treating physician if it is in the best interest of the patient after discussion with the PI. Concomitantly, the number of days of idarubicin will be reduced to **2 days** (Idarubicin 10 mg/m^2/day IV over 30-60 minutes on days 1-2).

Venetoclax Dosing (For Patients in Cohort 4 only)
Patients treated in cohort 4 (Frontline, untreated AML patients receiving the addition of venetoclax to CLIA) may receive venetoclax for 7 days of each cycle starting on approximately day 2 (with flexible window to allow delaying start up to day 5). Missed doses do not need to be made up. Rationale or reason for interruptions should be documented in the medical record.

Venetoclax levels in patients can be affected by concomitant use of strong CYP3A inhibitors. Because of the severe myelosuppression and immunosuppression that is present in patients with AML, antifungal prophylaxis and/or treatment is mandatory throughout their treatment. The vast majority of available options for antifungals in this setting are azoles, and are strong CYP3A inhibitors. Due to this reality, the concomitant use of azoles with venetoclax has been carefully studied, including pharmacokinetic evaluation. Recommended dose adjustments have been derived from these studies to match the target dose of venetoclax. Below is a table of recommended doses with and without concomitant use of moderate or strong CYP3A inhibitor that can be used as a guide. Dose level 1 is the starting dose for the study. Additional dose levels are provided for dose adjustment guidelines for subsequent cycles. Please refer to the venetoclax package insert for further details on drug-drug interactions.

Alternative dosing may be implemented based in individual patient situation after discussion with the PI and documentation of the rationale.

Venetoclax Dosing (PO Daily x 7 Days, starting approx. Day 2 (+ 3 day window)			
Dose Level	**Patients on strong CYP3A inhibitor**	**Patients on moderate CYP3A inhibitor**	**Patients not on CYP3A inhibitor**
-1	50 mg	100 mg	200 mg
1	100 mg	200 mg	400 mg

To establish tolerability and safety of the Venetoclax dose, a single escalation is planned based on the numbers of patients with a dose limiting toxicity (DLT). DLT is defined as a drug-related, clinically significant grade 3 or 4 non-hematologic toxicity. The higher dose that has fewer than 2 DLTs out of 6 patients will be the maximum tolerated dose (MTD). The first 3 evaluable patients will be treated at the -1 dose level of venetoclax. If this is deemed safe (i.e. no DLT in the 3 evaluable patients), the next 3 evaluable patients will be treated at dose level 1. If there is a single DLT at a dose level, the dose level will be expanded to 6 evaluable patients to confirm the safety. If there is a DLT in ≥ 2 patients out of 3 or 6 patients in a specific dose level, it will be considered above the MTD, and the dose level below will be considered the MTD as long as 6 patients have been treated at that dose level. If dose level -1 or 1 is considered the MTD, subsequent patients will be treated at this dose level. If dose level -1 is determined to be above the MTD, the protocol will be revised to include a lower dose/schedule of venetoclax to be evaluated based on the numbers, events, and grades of DLTs observed in doses -1 and 1.

CONSOLIDATION:
Cladribine 5 mg/m^2/day will be given IV over 1 to 2 hours on days 1-3 combined with cytarabine at a dose noted below IV over 2 hours daily on days 1-3. The cytarabine should be initiated approximately 3-6 hours following the start of the cladribine infusion. Idarubicin will be given at a dose of 8 mg/m^2/day IV over 30-60 minutes on days 1-2.

Consolidation – Cytarabine dose		
Age	**Cytarabine dose (cohorts 1-3)**	**Cytarabine dose (cohort 4 – addition of Venetoclax)**
Age < 60 years	1.5 grams/m^2	1 grams/m^2
Age > or = 60 years	1 grams/m^2	0.75 gram/m^2

One cycle of therapy is considered 4 weeks. Subsequent cycles may be started within 3-7 weeks after the start of the previous cycle depending on hematopoietic recovery (see section 6 for details) and resolution of toxicities in the judgment of the treating physician. Subsequent cycle delay beyond 7 weeks may be allowed after discussion with the principal investigator and documentation of the discussion.

Patients with progressive or proliferating disease requiring initiation of a subsequent cycle of chemotherapy prior to day 28 of a previous cycle may start therapy no earlier than day 21 of a previous cycle after discussion with the principal investigator and documentation of the discussion.

TARGETED THERAPY:

Approximately a third of patients with AML may harbor activating FLT3-ITD mutations. We have previously shown that combining sorafenib with chemotherapy in patients with FLT3-ITD mutations is both safe and efficacious. (Ravandi et. al. JCO 2010). Therefore, patients with known FLT3-ITD mutations will be allowed to receive sorafenib therapy at a dose of 400mg orally twice daily on days 1-14 during induction and then continuously for 28 days per cycle starting with cycle 2, at the discretion of the treating physician. Dose adjustments and interruptions of the sorafenib are per standard. The table below offers recommendations for dose-level adjustments, but other doses may be implemented per the discretion of the treating physician after discussion with the PI.

Recently, the phase III randomized double-blind RATIFY study was completed and reported for patients with FLT3 mutated AML (Stone RM, et al. NEJM 2017) . 717 patients with FLT3 mutated AML were randomized to receive araC + daunorubicin with or without midostaurin. Midostaurin led to a significant improvement in survival (median 74.7 months for midostaurin vs. 25.6 for placebo; P=0.007). Based on this study, midostaurin was approved for the treatment of patients with FLT3 mutated AML in combination with chemotherapy, the first combination to show a survival benefit in several decades. This has now become part of the standard of care in the treatment of FLT3-mutated AML. Midostaurin has the additional benefit of targeting not only FLT3-ITD mutations, but also point mutations in the FLT3 kinase, such as D835 mutations. Therefore, AML patients with known FLT3-ITD or FLT3 kinase domain mutations will be allowed to receive midostaurin at the recommended dose of 50mg orally twice daily on days 6-19 during induction, and then on days 6-19 during consolidation. Dose adjustments and interruptions of the midostaurin are per standard. The table below offers recommendations for dose-level adjustments, but other doses may be implemented per the discretion of the treating physician after discussion with the PI.

In November 2018, a new FLT3 inhibitor, gilteritinib, was approved by the FDA for patients with FLT-mutated AML. The approval was based on the ADMIRAL study, in which 138 patients with FLT3-mutated R/R AML were treated with gilteritinib at 120 mg PO daily. At a median followup of 4.6 months, the rate of complete remission (CR) and CR with partial hematologic recovery was 21% in a refractory population with a median age of 60 years. The drug was well tolerated, with the most common adverse events being myalgia, arthralgia, transaminitis, fatigue/malaise, diarrhea, edema, and rash. Pratz et al, recently presented their data studying the combination of gilteritinib with induction chemotherapy in patients ≥ 18 years with newly diagnosed FLT3 mutated AML. Patients were treated with idarubicin, cytarabine, and escalating doses of gilteritinib. A total of 66 patients, with a median age of 59.5 years was in the safety data set. The MTD and recommended phase II dose was found to be 120mg. The composite CR rate (CRc) was 94%, with 67% CR, 24% CR with incomplete count recovery (CRi), and 3% CRp. The median duration of remission was 14 months. There were no DLTs at the 120 mg dose. The most common treatment emergent AEs were febrile neutropenia, thrombocytopenia, anemia, sepsis, and increased ALT. The investigators concluded that the combination was safe and highly effective in FLT-mutated patients. Similar to midostaurin, gilteritinib is a Type I FLT3 inhibitor that has activity against both the

FLT3-ITD mutations as well as FLT3-D835. This therefore represents another important option for pts with FLT3-mutated AML. Patients may receive gilteritinib on D1-14 of the induction cycle and then continuously during consolidation cycles. The table below offers recommendations for dose-level adjustments, but other doses may be implemented per the discretion of the treating physician after discussion with the PI.

BCL-2 is a BH3-family anti-apoptotic protein that is overexpressed in hematologic malignancies and involved in chemoresistance and survival of the neoplastic clone. Small molecular "BH3-mimetics" have been developed to disrupt the interaction between anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1) and proapoptotic proteins (BAD, BAX, BIM). This disruption allows the release of proapoptotic proteins to initiate apoptosis via the intrinsic (mitochondrial) pathway. Venetoclax (ABT-199) is a highly-selective, orally bioavailable small molecule inhibitor of BCL-2 that has been shown to be highly active in BCL-2 dependent leukemia cell lines and primary patient samples. Venetoclax has also been shown to be safe and highly active as a single-agent in patients with chronic lymphocytic leukemia, and recently received FDA approval for this indication. Based on preclinical observations, venetoclax was also studied as a single-agent in patients with relapsed and refractory AML.[15] Promising single-agent activity has led to further investigation into combinations with chemotherapy in AML, described in the background section.

On November 21, 2018 venetoclax received accelerated FDA approval in combination with chemotherapy (5-azacytidine, decitabine, or low dose cytarabine) for older or unfit adults with previously untreated AML. Based on this, patients treated on cohort 4 of the protocol will be allowed the addition of venetoclax given at the designated dose on days 2-8 (+/- 1 day) of each cycle.

Patients with the presence of the Philadelphia chromosome [translocation (9;22)] or the presence of the bcr-abl fusion gene (detected by PCR or FISH) – such as those with CML myeloid blast phase or 'Philadelphia-positive AML' – may benefit from concomitant therapy with an abl tyrosine kinase inhibitor (TKI). Several orally bioavailable TKIs have now been FDA approved for Philadelphia positive CML and their selection is based on patient tolerance, comorbidities, and abl kinase domain mutations. Patients with bcr-abl positive disease may receive concomitant therapy with an approved TKI, dosed orally, continuously starting on day 1. The choice and dose will be per the discretion of the treating physician according to standard practice.

Suggested Sorafenib Dosing Adjustments	
Dose Level	Sorafenib Dose and Schedule
0	400 mg PO Twice Daily
-1	400 mg PO Once Daily
-2	200mg PO Once Daily
-3	200mg PO Once Every Other Day

Suggested Midostaurin Dosing Adjustments	
Dose Level	Midostaurin Dose and Schedule

0	50 mg PO Twice Daily
-1	50mg PO Once Daily
-2	50mg PO Every other Day

Suggested Gilteritinib Dosing Adjustments	
Dose Level	Gilteritinib Dose and Schedule
0	120 mg PO Daily
-1	80 mg PO Daily
-2	40 mg PO Daily

INTRATHECAL PROPHYLAXIS

Intrathecal prophylaxis with araC and/or methotrexate is standard in the therapy of acute lymphoblastic leukemia, but not currently a part of standard AML protocols. Patients with high risk disease, including those with WBC > 100 at presentation, those with LDH > 700, and those with FLT3(+) disease may be at higher risk of CNS (central nervous system) disease (Rosovski U, et. al. Leuk Lymph 2015). We will study the incidence of CNS disease at diagnosis in these patients as well as the effect of one dose of intrathecal cytarabine during the nadir of their blood counts, during cycle 1 or cycle 2.

Patients with a presenting WBC > 100 (documented either in MDACC or outside records) or FLT3(+) disease will be eligible to receive:

- **Cytarabine 100mg** in 3mL preservative-free normal saline x 1, administered via lumbar puncture (LP) or through Ommaya reservoir on Cycle 1 **day 21 +/- 7 days or cycle 2 day 14 +/- 7 days**. Peripheral WBC at the time of LP should be ≤ 1 and peripheral blasts should be ≤ 1%.

4.2 Supportive Care Measures during treatment

Necessary supportive measures for optimal medical care can be given throughout the study as indicated by the treating physician's assessment of the patient's medical need and by the institutional guidelines. Administration of antiemetics during drug administration and throughout treatment course is permitted as clinically indicated and according to departmental guidelines. Blood products should be transfused as indicated and in accordance with institutional guidelines. Concomitant intrathecal chemotherapy and/or radiation therapy is permitted where indicated in patients with extramedullary disease.

4.2.1 Hematopoeitic growth factors

Hematopoeitic growth factors such as filgrastim or pegfligrastim (GCSF) is permitted as clinically indicated at the discretion of the treating physician per department of leukemia standards.

4.2.2 Infection prophylaxis

Antibacterial, antifungal, and antiviral agents may be used in patients being treated on this study in accordance with the standard of care. Administration of venetoclax with strong CYP3A inhibitors such as posaconazole can predictably increase the plasma exposure of venetoclax. This has been studied in a pharmacokinetic study of venetoclax and posaconazole in leukemia patients.

Therefore, in practice, the dose of venetoclax in patients receiving azole antifungals is reduced as noted in the table found in Section 4.0. Patients with AML in our institution are almost universally treated with azole antifungal agents for prophylaxis and treatment. Therefore, we will recommend the recommended adjusted dosing given concomitantly with azole antifungals. Posaconazole has its own recommended venetoclax dose adjustment. Voriconazole is considered a strong CYP3A inhibitor; fluconazole and isavuconazonium are considered moderate CYP3A inhibitors.

4.2.3 Premedications/Precautions for chemotherapy

The following are recommended premedications for induction and consolidation chemotherapy:

- ondansetron 16mg IV daily on days of chemo

- methylprednisone 40mg IV daily prior each cytarabine dose

- prednisolone acetate 1% ophthalmic solution – 2 drops in each eye 4 times daily, each cycle. Start at the same time as the cytarabine infusion on Day 1 and continue for at least 2 days after the last dose of cytarabine.

Alternative strategies are allowed if clinically indicated.

4.2.4 Tumor lysis syndrome monitoring

Unlike CLL patients treated with venetoclax, the risk of tumor lysis in patients with AML treated with venetoclax has been low. Therefore, ramp-up dosing for venetoclax will not be implemented.

However, to mitigate any possible risk of tumor lysis syndrome for patients receiving venetoclax, several measures will be implemented:

a. Electrolyte levels, including serum potassium, calcium, phosphorous, and uric acid will be checked prior to treatment to make sure they are within the normal range. Hyperkalemia (Potassium > 5.0) should be corrected prior to starting therapy. Phosphate binders should be started (unless contraindicated) in patients with elevated phosphorous.

b. Patients with medium (WBC 10-20) risk for tumor lysis should be initiated on allopurinol (or other uric acid lowering treatment) prior to therapy. Patients with WBC > 20 should have cytoreduction (with hydrea) or delay therapy to make sure the WBC to less than 20 prior to starting therapy in protocol. If the uric acid is elevated above 9, the patient should be given a dose of rasburicase per institutional protocol.

c. Oral and when needed, intravenous hydration, will also be implemented per institutional standards to help mitigate the risk for tumor lysis syndrome.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse events, the treatment may be continued

for a total of 6 cycles. The patient will continue on the study unless one of the following criteria applies:

- Clinically significant progressive disease **(see section 9).**
- Allogeneic bone marrow transplant.
- Intercurrent illness that prevents further administration of treatment.
- Patient request.
- Unacceptable toxicity.
- Need for further, alternative treatment.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator or treating physician.

5.0 PATIENT EVALUATION

5.1 Pretreatment Evaluation. (To be completed within 14 days of study entry unless otherwise indicated)

a. History and physical examination, including vital signs, height, weight and performance status.
b. Bone marrow aspirate and/or biopsy within 28 days of treatment start.
c. Standard cytogenetics, flow cytometry and molecular studies if not done within 60 days.
d. CBC with differential (within 3 days) (differential not required if WBC $\leq 0.5 \times 10^9$/L).
e. Serum chemistry: BUN, creatinine, bilirubin, AST and/or ALT, Magnesium, glucose, uric acid, serum ferritin (within 3 days).
f. Urine pregnancy test within one week for women of childbearing potential.
g. In patients with no record of cardiac ejection fraction in previous 6 months, an echocardiogram or MUGA to confirm ejection fraction of > or = 45%.
h. Signed informed consent.

5.2 During treatment Evaluation.

a. Physical examination (including vital signs, weight, performance status) within 3 days prior to each cycle.
b. CBC with differential (differential not required if WBC $\leq 0.5 \times 10^9$/L), at least once weekly until remission, then every 2 to 4 weeks during active treatment, and then every 4 to 8 weeks thereafter as long as they are on study.
c. Serum chemistry profile at least once weekly until remission and then every 2 to 4 weeks during active treatment. Serum ferritin prior to each cycle.
d. Bone marrow aspiration and/or biopsy starting on day 28 (+/- 7 days) of

therapy and then as required by leukemia evolution until remission or non-response. Bone marrow tests may be ordered more frequently as indicated by changes in peripheral blood counts. No repeat bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC <0.4 $x10^9$/L, if the bone marrow is considered non-contributory by the investigator at any point.

e. Patients will be followed for survival every 6 to 12 months after completion of active treatment and while still on study or be enrolled on the leukemia department long-term follow-up umbrella protocol.

6.0 DOSING DELAYS / DOSE MODIFICATIONS FOR SUBSEQUENT CYCLES

6.1 Suggested dose levels for dose adjustments

Dose level	Cladribine (IV daily on days 1-5)*	Cytarabine < 60y (IV daily on days 1-5)*	Cytarabine ≥ 60y (IV daily on days 1-5)*	Idarubicin (IV daily on days 1-3)**
1	5 mg/m^2	2 gram/m^2 (1.5 g/m^2 †)	1.5 gram/m^2 (1 g/m^2 †)	10 mg/m^2 (8 mg/m^2†)
-1	4 mg/m^2	1.5 gram/m^2 (1 g/m^2 †)	1 gram/m^2 (0.75 g/m^2 †)	8 mg/m^2 (6 mg/m^2 †)
-2	3 mg/m^2	1 gram/m^2 (0.5 g/m^2 †)	.75 gram/m^2 (0.5 g/m^2 †)	6 mg/m^2 (4 mg/m^2 †)
-3	2 mg/m^2	0.5 grams/m^2 (0.25 g/m^2†)	0.5 grams/m^2 (0.25 g/m^2†)	4 mg/m^2 (3 mg/m^2 †)

* 3 days in consolidation
** 2 days in consolidation
† consolidation dose

Venetoclax Dosing (PO Daily x 7 Days , starting approx. day 2 (+ 3 day window)			
Dose Level	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on CYP3A inhibitor
-2	50mg x 3 days	50 mg	100 mg
-1	50 mg	100 mg	200 mg
1	100 mg	200 mg	400 mg

6.1.1. Dose levels different than dose described above may be allowed after discussion with the PI and documented in the patient's medical record.

6.1.2. Dose level of an individual drug can be modified independently of the others if a toxicity is considered related to a particular drug. For example: cytarabine and neurotoxicity, or idarubicin and cardiac toxicity. In cases of specific organ dysfunction such as liver and kidney, the following table can be used as guidance and different dose modifications may be implemented per the discretion of the treating physician after discussion with the PI .

Organ System	**Cladribine**	**Idarubicin**	**Cytarabine**
Creatinine (mg/dL)			
2.1 – 3	Reduce by 2 dose-levels	Reduce by 1 dose-level	Reduce by 1 dose-level
> 3	Discuss with PI		

Bilirubin (mg/dL)			
1.1 – 1.9	Maintain same dose	Maintain same dose	Maintain same dose
2.0 – 2.5	Maintain same dose	Reduce by 1 dose level	Maintain same dose
2.6 – 5	Maintain same dose	Reduce by 2 dose-levels	Maintain same dose level
> 5	Reduce by 2 dose-levels	OMIT	Reduce by 1 dose level

Non-Hematologic Toxicity	
Drug-related Grade 2 Toxicity Initiation of a treatment cycle may be delayed if a > Grade 1 drug-related clinically significant non-hematologic toxicity has occurred or worsened and not yet returned to < Grade 2 prior to the start of the next cycle. **Infection** If a patient develops a clinically significant infection of any grade,1 initiation of treatment cycles may be delayed or withheld until the infection is clinically controlled (e.g., the patient is afebrile and with improving signs/symptoms). Treatment (i.e., subsequent cycles) may then resume at the full dose. At the discretion of the investigator, prophylactic therapy to prevent recurrence of infection can be instituted as clinically indicated.	
Description of Event: Non-Hematologic	**Dose Modifications**
Drug-related clinically significant non-hematologic Grade 3-4 adverse event	Hold therapy until recovery to Grade ≤ 1, then re-start and reduce one dose level. If toxicity recurs again, hold therapy until recovery to grade ≤1, then re-start and reduce one dose level. Dose reductions below dose level -3 will be considered on an individual basis after discussion with the principal investigator. For adverse events that occur after the end of chemotherapy, dose reductions will take effect on the next cycle.
Persistent grade 2 toxicity considered clinically significant or upon patient's request	Consider holding therapy until recovery to Grade ≤ 1, then re-start and reduce one dose level. If toxicity recurs again, hold therapy until recovery to grade ≤1, then re-start and reduce one dose level. Dose reductions below dose level -3 will be considered on an individual basis after discussion with the principal investigator. For adverse events that occur after the end of chemotherapy, dose reductions may take effect on the next cycle.
Any occurrence of >/= drug related Grade 2 neurologic Events	The patient's study drug doses are to be re-evaluated in consultation with the Principal Investigator, and may be reduced according to the above parameters, or discontinued based on the event, and the time to resolution to </= Grade 1.

[1] Includes, but is not limited to, bacteremia, systemic fungal infections, cytomegalovirus (CMV) infection, *Pneumocystis carinii* pneumonia (PCP), disseminated *Varicella*, etc.

[2] Excludes NCI CTC >/= grade 2 drug-related neurologic toxicities, grade 2 alopecia, and grade 3 anorexia, transient elevations in hepatic transaminases or alkaline phosphatase based on institutional normals without clinical significance, and nausea/vomiting, diarrhea or mucositis that resolves (with or without supportive care) to < grade 2 within 48 hours of onset to grade 3.

[3] Excludes NCI CTC grade 4 transient elevations in hepatic transaminases or alkaline phosphatase based on institutional normals without clinical significance.

6.2 Patients in whom the toxicity occurs or persists beyond the planned completion of drug administration for the cycle will have the dose reductions implemented in subsequent cycles provided the toxicity has resolved as specified in the table above.

6.3 **Myelosuppression**: Patients with leukemias and MDS 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 and myelodysplastic syndromes. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 weeks of therapy. After this time, treatment interruptions and dose adjustments may be considered according to the following guidelines:

6.3.1 Patients with neutropenia or thrombocytopenia as a consequence of the disease do not require treatment interruptions for myelosuppression. Dose-reductions in these patients should be considered in an individual case and discussed with the PI. The following guidelines can be used for these patients:

6.3.1.1 Patients with a response and pre-cycle counts of neutrophils >1 $x10^9$/L and platelets >50 $x10^9$/L who have sustained low counts of neutrophils <0.5 $x10^9$/L or a platelet count <20 x $x10^9$/L for more than 4 consecutive weeks in the current cycle, may receive a subsequent course at 1 dose level reduction. A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.

6.3.1.2 If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts, continue treatment regardless of neutrophil and platelet count and give supportive care as needed.

6.3.1.3 If no marrow evidence of leukemia, hold therapy until recovery of granulocytes to ≥1 $x10^9$/L and platelets ≥ 60 $x10^9$/L, then resume at same or 1 lower dose level according to guidelines mentioned above.

6.4 Dose adjustments different than those described above may be considered in individual patients after discussion with the PI and proper documentation of the rationale.

7.0 AGENT FORMULATION AND PROCUREMENT

Cladribine, cytarabine, and idarubicin are all FDA approved and commercially available. Commercial supply will be used.

7.1 CORRELATIVE ANALYSIS

All patients will be approached for leukemia tissue banking protocol (LAB01-473: PI Steven Kornblau) and patients who consented for the protocol will provide extra bone marrow aspirate samples for the research use during the routine clinical bone marrow aspiration. There will be no extra biopsies for the research purpose and extra samples will be aspirated during the routine clinical biopsy. These samples will be stored at Leukemia Tissue Bank and will be used for correlative molecular studies including but not limited to DNA sequencing using the next generation sequencing platform (e.g. liquid tumor panel 300 [LTP300]), single-cell DNA/RNA sequencing (e.g. Tapestri platform, 10X Genome platform), methylation profiling, and RNA sequencing. These analysis will be done in collaboration with Koichi Takahashi and Andrew Futreal at Department of Genomic Medicine under the analysis protocol PA12-0305 and PA17-0645. These are

correlative exploratory analysis and the results will not be used to affect clinical management.

8.0 STATISTICAL CONSIDERATIONS

8.1 Preliminaries and Objectives

This is an open-label, 3-cohort, phase II trial of Cladribine plus Idarubicin + ARAC in patients as therapy for patients with AML, high risk MDS, or myeloid blast phase of CML. Patient cohorts will be based on whether patients are receiving frontline or salvage therapy, and, if frontline, whether they have de novo or secondary AML. Further, starting with the Venetoclax revisions, patients in the de novo frontline cohort will be divided into cohort 4 if they are able to receive Venetoclax or cohort 1 if not. Each patient in any cohort will be given induction therapy of cladribine 5mg/m^2/day over 2 hours with a 1-4 hour break before Cytarabine at 2 mg/m^2/day over 3 hours for days 1-5. Idarubicin will be given as 10 mg/m^2/day iv on days 1-3. Consolidation therapy will be similar doses of cladribine and Cytarabine, but given days 1-3. Idarubicin will be given as 8 mg/m^2/day IV on days 1-2. Venetoclax will be given as described in section 4, including a lead in safety-check with possible escalation of 1 dose level. The primary objective is to determine the complete response (CR) rate of this combination. Secondary objectives include assessing the overall response rate (ORR), overall survival (OS), event-free survival (EFS), duration of response, as well as the safety and tolerability. Exploratory correlative studies will be analyzed separately and described.

8.2 Endpoints

8.2.1 Primary Endpoint: Complete Response

Response will be measured according to Section 9.1 Criteria for Response. Patients will be classified as achieving a complete response if they have complete remission (CR) or complete remission without platelet recovery (CRi or CRp). Patients who do not have evidence of a complete response will be considered not to have a complete response, regardless of the reason, including early withdrawals for any reason.

8.2.2 Secondary Endpoints

8.2.2.2 Overall Response

Overall response is defined as CR, CRi, or partial remission (PR) according to section 9.1. Patients who do not have evidence of overall response will be considered to not have an overall response, regardless of the reason.

8.2.2.3. Overall Survival (OS)

OS is defined as the time from starting treatment until death from any cause. Patients who are alive at the time of analysis will be censored on the date of last contact.

8.2.2.4. Event-Free Survival (EFS)

EFS is defined as the time from starting treatment until disease recurrence, progression, or death, whichever comes first. Patients who are alive and free of progression/relapse will be censored on the last date of evaluation.

8.2.2.5. Duration of Response

Duration of response is defined as the time from first overall response is noted until progression or death, whichever comes first. Patients who do not have a response will not be included in this analysis. Patients who are alive without progression will be censored on the last date of evaluation.

8.2.2.6. Safety and Tolerability

Adverse events will be assessed according to NCI CTCAE 4.0. Date of start, date of resolution, grade, and attribution to study drug will be recorded.

8.2.2.7 Exploratory Endpoints

Patient and disease characteristics at trial entry, use of intrathecal prophylaxis, and incidence of leptomeningeal disease will be recorded.

8.3 Sample Size Justification

Up to 225 patients were planned to be enrolled, 75 patients in each cohort. With the revisions for a higher dose, we will stop enrollment from the original 225 with an estimated 158 patients (67 in the frontline cohort, 75 in the salvage cohort, and 16 patients in the s-AML cohort). With the higher dose, a new 50 patients per disease cohort will be added for a projected total of 308 patients, including the new 150 patients (2017 revision). With the new dose levels, we will use the same non-informative priors since the increased dose may present potential increases in toxicity which might reduce the opportunity for effective treatment to be delivered. Based on this subsequent revision in 2019, we will add a new *de novo* frontline cohort (4) to also enroll 50 patients. Additionally, since the *de novo* frontline cohort is performing well but meeting its accrual maximum, we are allowing additional enrollment in the original *de novo* frontline cohort (1) to allow treatment for those patient who are unable to receive venetoclax. The revised sample size for the original cohort 1 will be 100, based on patient access to this successful treatment while improving estimates in this population. For the *de novo* frontline cohort 1, if the trial continues to full size (100 patients) within the cohort, a posterior 95% credible interval (CI) of response will be (38.4%, 57.6%), assuming that the response is 0.45, a beta(0.9, 1.1) prior and 48/100 responses. For the 50 patients in the *de novo* frontline cohort 4, this sample size ensures that, if the trial continues to full size (50 patients) within the cohort, a posterior 95% credible interval (CI) of response will be (34.6%, 61.4%), assuming that the response is 0.45, a beta(0.9, 1.1) prior and 24/50 responses. In the secondary frontline cohort, a posterior 95% credible interval (CI) of response will be (15.3%, 36.6%), assuming that the response is 0.30, a beta(0.6, 1.4) prior and 15 responses. Similarly, in the salvage cohort, a posterior 95% credible interval (CI) of response will be (7.4%, 27.0%), assuming that the response is 0.15, a beta(0.3, 1.7) prior and 8 responses.

Justification of the original cohorts: For the de novo frontline cohort, this sample size ensures that, if the trial continues to full size within the cohort, a posterior 95% credible

interval (CI) of response will be (38.2%,60.3%), assuming that the response is 0.50, a beta(0.9, 1.1) prior and 37 responses. In the secondary frontline cohort, a posterior 95% credible interval (CI) of response will be (20.9%, 41.3%), assuming that the response is 0.30, a beta(0.6, 1.4) prior and 23 responses. Similarly, in the salvage cohort, a posterior 95% credible interval (CI) of response will be (7.7%, 23.3%), assuming that the response is 0.15, a beta(0.3, 1.7) prior and 11 responses.

8.4 Interim Monitoring New Higher Dose Cohorts

Interim analyses will be carried out separately for each of the cohorts with the new dose levels. Within cohort, monitoring will occur after every 10 patients have been evaluated to ensure that patients are exhibiting reasonable toxicity rates and response rates to continue with the trial. A Bayesian sequential monitoring design[30] will be used to monitor the trial for complete response and toxicity.

Complete response is defined in the endpoints section above. A patient becomes evaluable for response once the first response assessment is complete or once the patient leaves the trial without a response assessment. A patient off study without a response assessment will be considered evaluable with no complete response.

A trial limiting toxicity (TOX) is any grade 3 or higher non-hematologic toxicity that is at least possibly related to the study drug that occurs in the first cycle of therapy or death for any reason in the first 28 days.

Stopping rules and operating characteristics are based on boundaries and simulations performed in Multc Lean Desktop version 2.1.0.

8.4.1 Interim Analyses for Response and Toxicity in the *de novo* Frontline Cohort 1

In the original *de novo* cohort, at the time of the first protocol revision, there were 52 complete responses among 64 patients evaluable for response (81%) and only 2 patients with TOX events. The original dose is both effective and non-toxic in this cohort, so it is reasonable and conservative to start the higher dose cohort as a stand-alone cohort for monitoring.

Among the first 40 patients of the newer high dose patients in this cohort, 36 patients have CR/CRi and only 5 patient shave TOX events. With 36 patient with CR/CRi, there is no further need to check this arm for futility. The original futility rule was: For response, the trial will be stopped early if $Pr[\theta_R < 0.45 \mid data] > 0.95$, where θ_R denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 95% chance that the response rate is 45% or less, the trial will be stopped for futility. Implementing a constant rate of 45% for θ_R and a prior of ~beta(0.9,1.1) for this experimental treatment, pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table. Note, using these same methods in cohorts of 10 for 100 patients, the trial will continue if at least 32 out of 90 patients have CR/CRi, so no further futility checks will be made in this expanded cohort since 36 patients already have CR/CRi.

Under the same model described for response in the first 50 patients, toxicities will be

monitored based on a toxicity rate of 30%. Using the toxicity rate from the first 40 patients as the prior of beta(6, 34) for "standard" treatment and a prior of beta (0.6, 1.4) for this cohort. Safety will continue to be assessed for the additional patients. The cohort will be terminated if Prob(TOX > 0.15+0.15 | data) > 0.85. Following this rule, any cohort will be terminated according to the following table once the first 10 patients have enrolled.

Table for first 50 patients (using: Prob(TOX > 0.30 | data) > 0.95)

If there are this many evaluable patients in the cohort	**10**	**20**	**30**	**40**
Stop if there are this many patients *or fewer* with response	1	5	9	12
Stop if there are this many *or more* with TOX	6	10	14	18

Original Rules: If 0 or 1 of the first 10 evaluable patients respond to the treatment or if 6 or more have TOX events, stop the cohort and the treatment will be declared as ineffective or too toxic for this population. If there are at least 2 responses and 5 or fewer patients with TOX events, the next 10 patients will be entered in the study. Continue checking every 10. The operating characteristics are identical to those under Cohort 4.

Table for patients 51-100: (Using Prob(TOX > 0.15+0.15 | data) > 0.85)

If there are this many evaluable patients in the cohort	**50**	**60**	**70**	**80**	**90**
Stop if there are this many *or more* patients with TOX	20	24	27	31	35

Rules for Patients 51-100: If 20 or more of the first 50 patients have TOX events, stop the cohort and the treatment will be declared too toxic for this population. If 19 or fewer patients have TOX events, the next 10 patients will be entered in the study. Continue checking the numbers of patients with TOX events every 10 patients.

Operating Characteristics* for the Higher Dose *de novo* Frontline Cohort Patients 51-100 (Note, the original operating characteristics for patients 1-50 are identical to the operating characteristics table for Cohort 4)

	Stop if Stop if Prob(TOX > 0.15+0.15 | data) > 0.85		
True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.10	0.000	100.0	100 (100, 100)
0.20	0.001	99.9	100 (100, 100)
0.30	**0.13**	**94.5**	**100 (100, 100)**
0.40	0.75	66.5	50 (50, 90)
0.50	0.99	51.3	50 (50, 50)

*Operating characteristics are not conditioned on the first 40 patients, so probability of stopping early is overestimated at higher toxicities and the numbers of patients are slightly underestimated.

8.4.2 **Interim Analyses for Response and Toxicity in the Secondary Frontline Cohort**

In the original secondary frontline AML cohort, at the time of protocol revision, there were 5 complete responses among 14 patients evaluable for response (36%) and only 1 patient with any TOX events. The original dose is both effective and non-toxic in this cohort, so it is reasonable and conservative to start the higher dose cohort as a stand-alone cohort for monitoring.

For response, the trial will be stopped early if $Pr[\theta_R < 0.30 \mid data] > 0.95$, where θ_R denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 95% chance that the response rate is 30% or less, the trial will be stopped for futility. Implementing a constant rate of 30% for θ_R and a prior of ~beta(0.6,1.4) for this experimental treatment, pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table.

Under the same model described for response, toxicities will be monitored based on a constant toxicity rate of 30% and a prior of beta (0.6, 1.4) for this cohort. The cohort will be terminated if Prob(TOX > 0.30 | data) > 0.95. Following this rule, any cohort will be terminated according to the following table once the first 5 patients have enrolled.

If there are this many evaluable patients in the cohort	**10**	**20**	**30**	**40**
Stop if there are this many patients *or fewer* with response	0	2	5	7
Stop if there are this many *or more* with TOX	6	10	14	18

If 0 of the first 10 evaluable patients respond to the treatment or if 6 or more have TOX events, stop the cohort and the treatment will be declared as ineffective or too toxic for this population. If there is at least 1 response and 5 or fewer patients with TOX events, the next 10 patients will be entered in the study. Continue checking every 10 patients. The operating characteristics are summarized in the following table.

Operating Characteristics for the Higher Dose Secondary Cohort

		Stop if Prob{response < 0.30 | data} > 0.95 or Stop if Prob{DLT > 0.30 | data} > 0.95		
True Response Rate	True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.10	0.10	0.97	20.4	20 (10, 30)
0.20	0.10	0.54	16.5	40 (30, 50)
0.30	0.10	0.12	17.0	50 (50, 50)
0.40	0.10	0.01	49.6	50 (50, 50)
0.50	0.10	0.001	49.9	50 (50, 50)
0.10	0.20	0.97	20.4	20 (10, 20)
0.20	0.20	0.54	16.3	40 (30, 50)
0.30	0.20	0.12	46.7	50 (50, 50)

0.40	0.20	0.02	49.3	50 (50, 50)
0.50	0.20	0.01	49.6	50 (50, 50)
0.10	0.30	0.97	19.8	20 (10, 30)
0.20	0.30	0.58	34.6	30 (20, 50)
0.30	**0.30**	**0.20**	**44.2**	**50 (50, 50)**
0.40	0.30	0.11	46.5	50 (50, 50)
0.50	0.30	0.10	46.8	50 (50, 50)
0.10	0.40	0.98	18.1	20 (10, 20)
0.20	0.40	0.74	28.7	30 (10, 50)
0.30	0.40	0.51	35.3	40 (20, 50)
0.40	0.40	0.45	36.9	50 (20, 50)
0.50	0.40	0.44	37.1	50 (20, 50)
0.10	0.50	>0.99	15.4	10 (10, 20)
0.20	0.50	0.93	20.3	20 (10, 30)
0.30	0.50	0.87	23.0	20 (10, 30)
0.40	0.50	0.85	23.7	20 (10, 30)
0.50	0.50	0.85	23.8	20 (10, 30)

8.4.3 **Interim Analyses for Response in the Higher Dose Salvage Cohort**

In the original salvage cohort, at the time of protocol revision, there were 25 complete responses among 64 patients evaluable for response (39%) and 5 patients with any TOX events. The original dose is both effective and non-toxic in this cohort, so it is reasonable and conservative to start the higher dose cohort as a stand-alone cohort for monitoring.

For response, the trial will be stopped early if $Pr[\theta_R < 0.15 \mid data] > 0.975$, where θ_R denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 95% chance that the response rate is 15% or less, the trial will be stopped for futility. Implementing a constant rate of 15% for θ_R and a prior of ~beta(0.3,1.7) for this experimental treatment, pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table.

Under the same model described for response, toxicities will be monitored based on a constant toxicity rate of 30% and a prior of beta (0.6, 1.4) for this cohort. The cohort will be terminated if Prob(TOX > 0.30 | data) > 0.95. Following this rule, any cohort will be terminated according to the following table once the first 5 patients have enrolled.

If there are this many evaluable patients in the cohort	**10**	**20**	**30**	**40**
Stop if there are this many patients *or fewer* with response	x	0	1	2
Stop if there are this many *or more* with TOX	6	10	14	18

Even of 0 of the first 10 evaluable patients respond to the treatment, there is not sufficient

evidence to stop so there is no futility stop until 20 patients have been entered. However, if 6 or more have TOX events, stop the cohort and the treatment will be declared as too toxic for this population. If there are 5 or fewer patients with TOX events, the next 10 patients will be entered in the study. Continue checking every 10 patients. The operating characteristics are summarized in the following table.

Operating Characteristics for the Higher Dose Salvage Cohort

		Stop if Prob{response < 0.15 | data} > 0.975 or Stop if Prob{DLT > 0.30 | data} > 0.95		
True Response Rate	True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.05	0.10	0.72	33.3	30 (20, 50)
0.10	0.10	0.29	43.8	50 (40, 50)
0.15	0.10	0.08	48.1	50 (50, 50)
0.25	0.10	0.005	49.9	50 (50, 50)
0.35	0.10	<0.001	50.0	50 (50, 50)
0.05	0.20	0.73	33.2	30 (20, 50)
0.10	0.20	0.29	43.5	50 (40, 50)
0.15	0.20	0.09	47.8	50 (50, 50)
0.25	0.20	0.01	49.6	50 (50, 50)
0.35	0.20	0.01	49.7	50 (50, 50)
0.05	0.30	0.75	31.7	30 (20, 40)
0.10	0.30	0.36	41.2	50 (30, 50)
0.15	**0.30**	**0.17**	**45.2**	**50 (50, 50)**
0.25	0.30	0.10	46.8	50 (50, 50)
0.35	0.30	0.10	46.9	50 (50, 50)
0.05	0.40	0.85	27.0	20 (20, 40)
0.10	0.40	0.60	33.4	30 (20, 50)
0.15	0.40	0.49	36.0	50 (20, 50)
0.25	0.40	0.44	37.1	50 (20, 50)
0.35	0.40	0.44	37.2	50 (20, 50)
0.05	0.50	0.96	20.0	20 (10, 20)
0.10	0.50	0.89	22.4	20 (10, 30)
0.15	0.50	0.86	23.4	20 (10, 30)
0.25	0.50	0.85	23.7	20 (10, 30)
0.35	0.50	0.85	23.8	20 (10, 30)

8.4.4 **Interim Analyses for Response and Toxicity in the *de novo* Frontline Cohort 4**

The frontline cohort receiving venetoclax will follow the same rules as the first 50 patients from cohort 1 described above. Briefly, the trial will be stopped early if $Pr[\theta_R < 0.45 \mid data] > 0.95$, or if $Prob(TOX > 0.30 \mid data) > 0.95$.

If there are this many evaluable patients in the cohort	**10**	**20**	**30**	**40**
Stop if there are this many patients *or fewer* with response	1	5	9	12
Stop if there are this many *or more* with TOX	6	10	14	18

If 0 or 1 of the first 10 evaluable patients respond to the treatment or if 6 or more have TOX events, stop the cohort and the treatment will be declared as ineffective or too toxic for this population. If there are at least 2 responses and 5 or fewer patients with TOX events, the next 10 patients will be entered in the study. Continue checking every 10. The operating characteristics are summarized in the following table.

Operating Characteristics for the Higher Dose *de novo* Frontline Cohort 4

		Stop if Prob{response < 0.45 | data} > 0.95 or Stop if Prob{DLT > 0.30 | data} > 0.95		
True Response Rate	True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.30	0.10	0.69	30.9	30 (20, 50)
0.40	0.10	0.24	43.5	50 (50, 50)
0.45	0.10	0.11	47.0	50 (50, 50)
0.50	0.10	0.04	48.8	50 (50, 50)
0.55	0.10	0.01	49.6	50 (50, 50)
0.30	0.20	0.69	30.8	30 (20, 50)
0.40	0.20	0.25	43.2	50 (40, 50)
0.45	0.20	0.12	46.7	50 (50, 50)
0.50	0.20	0.05	48.5	50 (50, 50)
0.55	0.20	0.02	49.3	50 (50, 50)
0.30	0.30	0.72	29.4	30 (20, 50)
0.40	0.30	0.32	40.9	50 (30, 50)
0.45	**0.30**	**0.20**	**44.2**	**50 (50, 50)**
0.50	0.30	0.14	45.8	50 (50, 50)
0.55	0.30	0.11	46.5	50 (50, 50)
0.30	0.40	0.83	25.1	20 (10, 30)
0.40	0.40	0.58	33.0	30 (20, 50)
0.45	0.40	0.50	35.3	40 (20, 50)
0.50	0.40	0.46	36.4	50 (20, 50)
0.55	0.40	0.45	36.9	50 (20, 50)
0.30	0.50	0.95	18.7	20 (10, 20)

0.40	0.50	0.88	22.1	20 (10, 30)
0.45	0.50	0.86	23.0	20 (10, 30)
0.50	0.50	0.85	23.5	20 (10, 30)
0.55	0.50	0.85	23.7	20 (10, 30)

8.5 Interim Monitoring Original Cohorts (Stopped before completion due to Dose Change – 2017)

Interim analyses will be carried out separately for each cohort. Within cohort, monitoring will begin after 5 patients have been enrolled and will then be performed continuously (monthly) to ensure that patients are exhibiting reasonable toxicity rates and response rates to continue with the trial. A Bayesian sequential monitoring design[30] will be used to monitor the trial for response and toxicity. The toxicity stopping rules are described in section 8.4.3. Stopping rules and operating characteristics are based on boundaries and simulations performed in Multc Lean Desktop version 2.1.0.

8.4.1 **Interim Analyses for Response in the Original Dose do novo Frontline Cohort**

For response, the trial will be stopped early if $Pr[\theta_R < 0.45 \mid data] > 0.90$, where θ_R denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 90% chance that the response rate is 45% or less, the trial will be stopped for futility. Implementing a constant rate of 45% for θ_R and a prior of ~beta(0.9,1.1) for this experimental treatment, pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table. Once 5 patients have been enrolled, follow the instructions in this table every month.

If there are this many (or more) patients with complete response assessments in the cohort	Stop if there are this many or fewer responses
5	0
6	1
9	2
12	3
15	4
17	5
20	6
23	7
25	8
28	9
30	10
33	11
36	12
38	13
41	14
43	15
46	16

48	17
50	18
53	19
55	20
58	21
60	22
63	23
65	24
68	25
70	26
72	27

Assuming the cohort does not stop for toxicity first, 5 patients will be accrued and followed for response. A patient becomes evaluable once the first response assessment is complete or once the patient leaves the trial without a response assessment. A patient off study without a response assessment will be considered evaluable with no complete response. If 0 of the 5 evaluable patients respond to the treatment, stop the cohort and the treatment will be declared as ineffective for this population. If there is at least 1 response, the next patient will be entered in the study stopped according to the toxicity boundaries below. Continue checking every month for sufficient responses assuming the cohort does not stop for toxicity first. The operating characteristics for efficacy are summarized in the following table. These assume the toxicity is either 10% or 25% so unlikely or possible to stop the trial due to toxicity.

The operating characteristics for efficacy based on Multc Lean are shown in the following table.

		Stop if Prob{response < 0.45 | data} > 0.90		
True Response Rate	True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.30	0.10	0.97	17.3	9 (6, 23)
0.40	0.10	0.66	39.1	30 (9, 75)
0.45	0.10	0.41	51.4	75 (15, 75)
0.50	0.10	0.23	60.7	75 (75, 75)
0.55	0.10	0.13	66.8	75 (75, 75)
0.30	0.25	0.98	15.2	9 (5, 17)
0.40	0.25	0.73	32.7	17 (6, 75)
0.45	0.25	0.55	42.5	43 (6, 75)
0.50	0.25	0.41	49.9	75 (10, 75)
0.55	0.25	0.32	54.7	75 (15, 75)

8.4.2 **Interim Analyses for Response in the Original Dose Secondary Frontline Cohort**

For response, the cohort will be stopped early if $Pr[\theta_R < 0.30 \mid data] > 0.90$, where θ_R denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 90% chance that the response rate is 30% or less, the cohort will be stopped for futility. Implementing a constant rate of 30% for θ_R and a prior of ~beta(0.6, 1.4) for this experimental treatment, pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table. Once 5 patients have been enrolled, follow the instructions in this table every month.

If there are this many (or more) patients with complete response assessments in the cohort	Stop if there are this many or fewer responses
5	0
9	1
14	2
18	3
22	4
26	5
31	6
35	7
39	8
43	9
46	10
50	11
54	12
58	13
62	14
66	15
69	16
73	17

Assuming the cohort does not stop for toxicity first, 5 patients will be accrued and followed for response. A patient becomes evaluable once the first response assessment is complete or once the patient leaves the trial without a response assessment. A patient off study without a response assessment will be considered evaluable with no complete response. If none of the 5 evaluable patients respond to the treatment, stop the cohort and the treatment will be declared as ineffective for this population. If there is at least 1 response, the next patient will be entered in the unless the cohort is stopped according to the toxicity boundaries below. Continue checking every month for sufficient responses assuming the trial does not stop for toxicity first. The operating characteristics for efficacy are summarized in the following table. These assume the toxicity is either 10% or 25% so unlikely or possible to stop the trial due to toxicity.

The operating characteristics for efficacy based on Multc Lean are shown in the following table.

True Response Rate	True Toxicity Rate	Stop if Prob{response < 0.30 | data} > 0.90		
		Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.20	0.10	0.92	22.3	9 (5, 31)
0.25	0.10	0.71	35.5	22 (5, 75)
0.30	0.10	0.45	48.8	75 (9, 75)
0.35	0.10	0.26	58.7	75 (46, 75)
0.40	0.10	0.15	65.1	75 (75, 75)
0.20	0.25	0.94	19.3	9 (5, 22)
0.25	0.25	0.78	29.8	14 (5, 62)
0.30	0.25	0.58	40.4	31 (5, 75)
0.35	0.25	0.43	48.3	75 (9, 75)
0.40	0.25	0.34	53.4	75 (13, 75)

8.4.3 **Interim Analyses for Response in the Original Dose Salvage Cohort**

The same monitoring methods will be used to monitor response in this cohort. The cohort will be stopped early if $Pr[\theta_R < 0.15 \mid data] > 0.90$, where θ_R denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 90% chance that the response rate is 15% or less, the cohort will be stopped for futility. Implementing a constant rate of 15% for θ_R and a prior for this experimental treatment of ~beta(0.3,1.7), pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table. Once 5 patients have been enrolled, follow the instructions in this table

Update to 75 patients

If there are this many (or more) patients with complete response assessments in the cohort	5	17	27	36	45	53	62	70
Stop if there are this many or fewer responses	0	1	2	3	4	5	6	7

Assuming the cohort does not stop for toxicity first, 5 patients will be accrued and followed for response. A patient becomes evaluable once the first response assessment is complete or once the patient leaves the trial without a response assessment. A patient off study without a response assessment will be considered evaluable with no complete response. If 0 of the 5 evaluable patients respond to the treatment, stop the cohort and the treatment will be declared as ineffective for this population. If there is at least 1 response, the next 12 patients will be entered in the cohort, unless they need to stop according to the toxicity boundaries below. Continue checking every month for sufficient responses assuming the cohort does not stop for toxicity first. The operating characteristics for efficacy are summarized in the following table. These assume the toxicity is either 10% or 25% so unlikely or possible to stop due to toxicity.

The operating characteristics for efficacy based on Multc Lean are shown in the following table.

True Response Rate	True Toxicity Rate	Stop if Prob{response < 0.15 | data} > 0.90		
		Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.05	0.10	0.99	10.3	5 (5, 5)
0.10	0.10	0.85	22.7	5 (5, 36)
0.15	0.10	0.59	37.6	17 (5, 75)
0.20	0.10	0.39	49.1	75 (5, 75)
0.25	0.10	0.26	56.9	75 (17, 75)
0.05	0.25	0.99	9.4	5 (5, 5)
0.10	0.25	0.89	19.4	5 (5, 27)
0.15	0.25	0.68	31.3	5 (5, 75)
0.20	0.25	0.53	40.5	35 (5, 75)
0.25	0.25	0.43	46.8	75 (5, 75)

8.4.4 **Interim Analyses for Toxicity all Original Dose Cohorts**

Under the same model described for response, toxicities will be monitored based on a constant toxicity rate of 30% and a prior of beta (0.6, 1.4) for this cohort. A trial limiting toxicity (TOX) is any grade 3 or higher non-hematologic toxicity that is at least possibly related to the study drug that occurs in the first cycle of therapy or death for any reason in the first 28 days. The cohort will be terminated if Prob(TOX > 0.30 | data) > 0.85. Following this rule, any cohort will be terminated according to the following table once the first 5 patients have enrolled.

If there are this many patients with TOX	Stop the cohort if there are this many (or fewer) patients who are evaluable (have TOX or completed the first cycle without TOX)
3	5
4	7
5	10
6	13
7	16
8	18
9	21
10	24
11	27
12	30
13	33
14	36

15	39
16	42
17	45
18	48
19	51
20	54
21	57
22	60
23	63
24	66
25	69
26	72
27	75*

*The trial will stop at 75 regardless of the number of patients with TOX. However, if there are 27 or more patients with TOX in a cohort, then that cohort is too toxic for further investigation.

Five patients will be accrued before the first analysis. If 3 of the 5 patients have DLTs, stop the trial and the treatment will be declared as too toxic for this population. If there are 2 or fewer DLTs, monitor this table each month. The operating characteristics for toxicity are summarized in the following table. These assume the response is either 20% or 30% for the salvage cohort; 50% or 60% in the frontline de novo cohort; and 40% and 50% in the frontline secondary cohort, so unlikely but possible to stop the cohort due to poor response.

The operating characteristics for toxicity are shown in the following table.

		Stop if Prob{DLT > 0.30 | data} > 0.85		
True Toxicity Rate	True Response Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
Salvage Cohort				
0.15	0.20	0.40	47.9	75 (5, 75)
0.25	0.20	0.53	40.5	35 (5, 75)
0.30	0.20	0.67	33.0	13 (5, 75)
0.35	0.20	0.83	24.3	7 (5, 39)
0.40	0.20	0.94	16.7	5 (5, 18)
0.15	0.30	0.21	60.8	75 (75, 75)
0.25	0.30	0.37	51.1	75 (5, 75)
0.30	0.30	0.56	41.1	39 (5, 75)
0.35	0.30	0.77	29.9	13 (5, 63)
0.40	0.30	0.93	20.0	9 (5, 27)
Frontline Cohort de novo				
0.15	0.50	0.25	59.3	75 (60, 75)

0.25	0.50	0.41	49.9	75 (10, 75)
0.30	0.50	0.58	40.5	33 (6, 75)
0.35	0.50	0.79	29.5	15 (5, 57)
0.40	0.50	0.93	19.9	10 (5, 26)
0.15	0.60	0.10	68.6	75 (75, 75)
0.25	0.60	0.28	57.6	75 (30, 75)
0.30	0.60	0.49	46.5	75 (10, 75)
0.35	0.60	0.74	33.4	21 (6, 75)
0.40	0.60	0.92	22.1	12 (5, 30)
Frontline Cohort Secondary AML				
0.15	0.40	0.17	63.5	75 (75, 75)
0.25	0.40	0.34	53.4	75 (13, 75)
0.30	0.40	0.54	43.2	48 (7, 75)
0.35	0.40	0.77	31.2	16 (5, 66)
0.40	0.40	0.92	20.9	10 (5, 29)
0.15	0.50	0.08	69.5	75 (75, 75)
0.25	0.50	0.27	58.4	75 (39, 75)
0.30	0.50	0.49	47.1	75 (10, 75)
0.35	0.50	0.73	33.8	21 (5, 75)
0.40	0.50	0.91	22.4	12 (5, 32)

8.6 Analysis Plan

Patients' demographic information at baseline will be analyzed, with data summarized in tables listing the number and percentages. Overall complete response (CR + CRi) rates and their 95% credible intervals will be estimated using a beta distribution with a prior of Beta (0.3, 1.7) for salvage patients and a prior of Beta (0.6, 1.4) for frontline patients with secondary AML and a prior of Beta (0.9, 1.1) for de novo frontline patients. OS, EFS, and duration of response will be estimated using the Kaplan-Meier method [29]. Overall response (CR+CRi+PR), adverse events, and exploratory relationships will be summarized by descriptive tables and figures. With the additional cohorts added at a higher dose, each disease and dose cohort will be reported separately for a total of 7 dose and disease cohorts. The posterior probability that the CR rate is higher in the higher dose cohorts will be computed separately for each of the original 3 disease cohorts.

8.7 Study Accrual and Duration

The maximum number of patients will be 408, with varying sizes in the original cohorts totaling 158 patients and 250 at the higher doses (100 in the frontline *de novo* cohort 1 and 50 in the remaining 3 cohorts. . The accrual rate will be 4-5 patients per month, with frontline patients accruing faster due to competing trials for the other cohorts. The length of follow-up will be until all patients either 1) have completed induction and consolidation up to 6 total cycles and final response assessment or 2) have been withdrawn from the study prior to completion.

9.0 MEASUREMENT OF EFFECT

9.1 Criteria for Response

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for response. Patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

9.1.2 Response Criteria

Response Criteria are according to the Revised Recommendations of the International Working Group Response Criteria in Acute Myeloid Leukemia. They are summarized below.

9.1.3 Complete remission (CR)

Disappearance of all clinical and/or radiologic evidence of disease, including extramedullary leukemia. Neutrophil count $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, and bone marrow differential showing $\leq 5\%$ blasts.

9.1.4 Complete remission without platelet recovery (CRi)

Have met all criteria for CR, except for either residual neutropenia (ANC $< 1.0 \times 10^9$/L) or thrombocytopenia (platelet count $< 100 \times 10^9$/L).

9.1.5 Partial remission (PR)

Blood count recovery as for CR, but with a decrease in marrow blasts of at least 50% and not more than 6 to 25% abnormal cells in the bone marrow.

9.1.6 Event-free survival (DFS)

Time from date of treatment start until the date of first objective documentation of disease-relapse or death.

9.1.7 Overall survival (OS)

Time from date of treatment start until date of death due to any cause.

9.1.8 **Disease progression**

Progression will be defined as recurrence of the disease necessitating change in therapy, or failure to respond to therapy requiring change in treatment.

10.0 EGULATORY AND REPORTING REQUIREMENTS

10.1 Regulatory and Reporting Requirements

CTCAE term (AE description) and grade: The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

Refer to Section 10.2 for Leukemia-Specific Adverse Event Recording Guidelines. The Principal Investigator will sign the PDMS. Case Report Form toxicity pages per each patient at the completion of each course. Following signature, the Case Report Form will be used as source documentation for the adverse events.

10.2 Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE-**"** All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment" and Guideline for Good Clinical Practice 4.11.1 "All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting".

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.

Adverse Events (AEs) will be evaluated according to current CTC version in each protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:

1. *Myelosuppression related events (due to disease or leukemia therapy)*
    a. *febrile or infection episodes not requiring management in the intensive care unit*
    b. *epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage*
    c. *anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis*
2. *Disease related events*
    a. *symptoms associated with anemia*
        i. *fatigue*
        ii. *weakness*
        iii. *shortness of breath*
    b. *electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)*
    c. *chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)*
    d. *coagulation abnormalities*
    e. *disease specific therapy (induction, maintenance, salvage, or stem cell therapy)*
    f. *alopecia*
    g. *bone, joint, or muscle pain*
    h. *liver function test abnormalities associated with infection or disease progression*
    i. *disease progression*
3. *General therapy related events*
    a. *catheter related events*
    b. *renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy*
    c. *rash related to antibiotic use*
4. ***Hospitalization for the management of any of the above expected events***

Abnormal hematologic values will not be recorded on the CRF. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

Serious Adverse Event Reporting (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- 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).

It is the responsibility of the PI and the research teams 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.

Reporting of external SAEs

- The MDACC institutional policy for reporting of external SAEs will be followed.

11.0 REFERENCES

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