A phase II study of azacitidine, venetoclax and trametinib for patients with acute myeloid leukemia or higher-risk myelodysplastic syndrome

Principal Investigator:

Nicholas Short, MD
Department of Leukemia,
University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard Unit 428
Houston, Texas 77030
Tel – 713-563-4485
E-mail – nshort@mdanderson.org

Co-Principal Investigator:

Farhad Ravandi, MD
Department of Leukemia,
University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard Unit 428
Houston, Texas 77030
Tel – 713-745-0394
E-mail – fravandi@mdanderson.org

TABLE OF CONTENTS

1. INTRODUCTION

For older patients who cannot tolerate intensive chemotherapy, single agent hypomethylating agents such as azacitidine or decitabine are commonly used based on studies showing that they improve survival compared to low-dose cytarabine or supportive care alone.[1,2] More recently, the combination of the Bcl-2 inhibitor venetoclax with a hypomethylating agent is emerging as a new standard of care for older patients with newly diagnosed AML who are unfit for standard intensive chemotherapy.[3,4] An ongoing study is evaluating the safety and efficacy of venetoclax in combination with either decitabine or azacitidine for patients ≥65 years of age with previously untreated AML and who are ineligible for chemotherapy.[4] At the most recent update, 145 patients were treated with a median age of 74 years (range, 65-86 years). Cytogenetics were poor risk in 49% of patients. The 30-day and 60-day mortality rates were 3% and 8%, respectively. The complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate for the entire cohort was 66% with a median duration of CR/CRi of 11.0 months. The median overall survival (OS) for the entire cohort was 17.5 months, and the 1 year-OS rate was 59%. These results represent the best survival data for older, unfit patients with newly diagnosed AML yet reported. A subsequent phase III study of venetoclax plus azacitidine versus azacitidine alone showed a significant improvement in OS in the azacitidine and venetoclax arm, although data have not yet been presented.

Several retrospective studies have been published evaluating the safety and efficacy of venetoclax plus a hypomethylating agent in patients with relapsed/refractory AML. A study from MD Anderson evaluated the outcomes of 43 patients with relapsed/refractory myeloid malignancies (n=39, 91% with AML) who received venetoclax in combination with other agents.[5] Thirty-one of the evaluated patients (72%) received venetoclax with a hypomethylating agent. Most patients (84%) were treated in salvage 2 or later (range 2-8) with a median of 3 prior treatment regimens. Objective response rate (ORR) was achieved in 9 (21%) patients, including 2 (5%) with CR, 3 (7%) with CRi, and 4 (9%) with morphologic leukemia-free state (MLFS). Of the 9 responding patients, all responded within 1 cycle of venetoclax combination therapy. These nine responding patients included eight (26%) of the patients treated with an HMA combination. With a median follow-up of 3 months, the estimated 6-month OS rate was 24%. In another study of venetoclax in combination with hypomethylating agents in relapsed/refractory AML from City of Hope, 33 patients were treated.[6] The median number of prior therapies was 2 (range, 1-8). Twenty patients (61%) had failed HMA therapy previously and 13 patients (39%) had prior allogenic stem cell transplantation. The ORR was 64% (N=21), with 10 patients (30%) achieving CR, 7 (21%) achieving CRi and 4 (12%) achieving MLFS. With a median follow-up of 6.5 months, the 1-year OS rate was 53%. The group at Memorial Sloan Kettering Cancer Center has also reported their experience with venetoclax in combination with either low-dose cytarabine or a hypomethylating agent in patients with R/R myeloid malignancies.[7] A total of 24 patients were treated (n=8 with hypomethylating agent; N=16 with low-dose cytarabine). Twenty-three patients (96%) had a diagnosis of AML. The median number of prior treatments was 3 (range, 1-8); 6 patients (29%) had prior stem cell transplantation. Of 21 patients evaluable for efficacy, the ORR was 29%, including a CR rate of 24% (n=5) and PR rate of 5% (n=1). With a median follow-up of 4.1 months, the 3-month OS rate was 72%.

Despite the promising results with azacitidine plus venetoclax, the development of resistance is common. The addition of novel agents to chemotherapy or hypomethylating agent backbone regimens may improve outcomes for patients with AML.[8] One major driver of resistance in patients treated with venetoclax-based combinations is alteration of the MAPK signaling pathway. For example, mutations in *KRAS* or *NRAS* are present in 10-25% of patients at the time of diagnosis and are associated with a lower likelihood of response to hypomethylating agent plus venetoclax combinations.[9,10] New treatment-emergent Ras pathway-activing mutations (e.g. mutations in *FLT3*, *NRAS/KRAS*, *PTPN11*, etc.) are also commonly observed at the time of relapse in these patients.[11] The development of effective therapies capable of producing long-term remissions in this population of patients with AML harboring Ras pathway-activating mutations is an unmet need. Given the high frequency of Ras-activating mutations at relapse and their role in both primary and

secondary venetoclax resistance, combination strategies that incorporate agents that target this signaling pathways before the development of resistance may help to delay or prevent relapse. Preclinical studies suggest that dual targeting of BCL2 and the MAPK pathway may be synergistic in the treatment of AML.[12]

Trametinib is an oral MEK inhibitor that is FDA approved (in combination with the BRAF inhibitor dabrafenib) for malignant melanoma, non-small cell lung cancer, and anaplastic thyroid cancer that harbors a *BRAF* mutation. Trametinib has also shown clinical activity in patients with relapsed/refractory AML harboring a *RAS* mutation. In a phase I/II study from MD Anderson, the toxicity profile of trametinib was consistent with that reported in the solid tumor literature.[13] The recommended phase 2 dose of trametinib was 2mg daily. In patients with relapsed/refractory AML or MDS with an *NRAS* or *KRAS* mutation, trametinib monotherapy resulted in an overall response rate of 20%, and the overall response rate was 27% in patients with CMML with an *NRAS* or *KRAS* mutation. Given the single-agent activity of trametinib in *RAS*-mutated AML, combination strategies that incorporate trametinib for patients with RAS mutations are warranted.

We therefore propose of a phase II study of the combination of azacitidine, venetoclax and trametinib for patients with relapsed/refractory AML or high-risk MDS harboring Ras pathway-activating mutations. Given the established role of Ras pathway-activating mutations in primary or secondary resistance to venetoclax monotherapy or hypomethylating agent plus venetoclax combinations,[11,14] there is also a rationale for early integration of MEK inhibition prior to the development of acquired Ras pathway mutations. The goal of this approach is to prevent (or delay) the emergence of venetoclax-resistant *RAS*-mutated subclones that contribute to relapse. In the present study we therefore propose to also evaluate the combination of azacitidine, venetoclax, and trametinib in patients with newly diagnosed AML irrespective of *RAS* mutation status, with the goal of prolonging remission durations and survival through prevention of treatment-emergent Ras pathway mutations. This frontline cohort would be opened only after safety is established in a safety lead-in of patients with relapsed/refractory AML or high-risk MDS.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

- Cohort A: To determine overall survival rate at 1 year of the regimen in patients with newly diagnosed AML
- Cohort B: To determine the complete remission(CR)/Complete remission without recovery of counts (CRi)/morphologic leukemia-free state (MLFS) rate of the regimen in patients with relapsed/refractory AML or high-risk MDS

2.2 Secondary Objectives

- To assess other efficacy endpoints (CR rate, minimal residual disease negativity by flow cytometry, relapse-free survival, event-free survival, and overall survival)
- To assess proportion of patients proceeding to HSCT
- To determine the safety of the combination regimen

2.3 Exploratory Objectives

- To evaluate the impact of baseline genomic alterations on response and survival of the combination regimen
- To evaluate clonal evolution from diagnosis to relapse

3. SELECTION OF PATIENTS

Patients will be selected from those referred to the Leukemia department at M D Anderson Cancer Center through the normal of process of referral. Eligible patients will be registered after the process of consenting on the MD Anderson protocol and data monitoring system.

3.1 Inclusion Criteria

1. Diagnosis:
   a) Cohort A (frontline): Adults ≥18 years with newly diagnosed AML.
   b) Cohort B (relapsed/refractory): Adults ≥18 years with relapsed/refractory AML or relapsed/refractory MDS or CMML that is intermediate-2 or high-risk by the International Prognostic Scoring System with ≥10% blasts harboring a Ras pathway-activating mutation. *Eligible mutations include: activating mutations of KIT, HRAS/NRAS/KRAS, BRAF, CBL or PTPN11 or loss of function mutation of NF1. Other mutations not listed here that are anticipated to activate Ras signaling may be considered for enrollment after discussion with the PI.*

2. Performance status ≤2 (ECOG Scale).

3. Adequate liver and renal function as defined by the following criteria:
   a) Total serum bilirubin ≤ 2.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome, hemolysis or the underlying leukemia approved by the PI
   b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 3 x ULN, unless due to the underlying leukemia approved by the PI
   d) Creatinine clearance ≥30 mL/min

4. Ability to swallow

5. Signed informed consent

3.2 Exclusion Criteria

1. Patients suitable for and willing to receive intensive induction chemotherapy (cohort A only)

2. Active serious infection not controlled by oral or intravenous antibiotics (e.g. persistent fever or lack of improvement despite antimicrobial treatment).

3. Patients with a prior or concurrent malignancy whose natural history or treatment is not anticipated to interfere with the safety or efficacy assessment of the investigational regimen may be included only after discussion with the PI

4. Consumed strong inducer of CYP3A or p-glycoprotein within 3 days of study enrollment. Agents include but are not limited to: carbamazepine, phenytoin, rifampin, and St. John's wart.

5. Treatment with any investigational antileukemic agents or chemotherapy agents in the last 7 days before study entry, unless full recovery from side effects has occurred or patient has rapidly progressive disease judged to be life-threatening by the investigator.

Prior recent treatment with corticosteroids, hydroxyurea and/or cytarabine (given for cytoreduction) permitted.

6. Pregnant women will not be eligible; women of childbearing potential should have a negative pregnancy test prior to entering on the study and be willing to practice methods of contraception throughout the study period and for at least 6 months after the last dose of study drugs. Women do not have childbearing potential if they have had a hysterectomy or are postmenopausal without menses for 12 months. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control throughout the study period and for at least 4 months after the last dose of study drugs. Lactating women (or those planning to breastfeed) should not breastfeed during treatment of trametinib and for at least 2 months after the last dose of trametinib.

4. TREATMENT OF SUBJECTS

4.1. Variations in doses of the study agents or supportive care medications or dose schedules other than those suggested below are allowed if deemed to be in the best interest of patients. Such changes should be discussed with the PI before they are instituted.

4.2. **Treatment Overview** – This will be a phase II, single-arm, open-label study conducted solely at MD Anderson Cancer Center. There will be an initial safety lead-in of 6 patients with relapsed/refractory AML. Patients with newly diagnosed AML will not be enrolled until safety of the combination is confirmed during this safety lead-in.

Cohort A will enroll patients with newly diagnosed AML and Cohort B will enroll patients with relapsed/refractory AML or higher-risk MDS or CMML.

The regimen consists of up to 24 cycles of the combination of azacitidine, venetoclax, and trametinib. Each cycle is anticipated to be 28 days in length, although cycle delays may be made due to delayed count recovery, intercurrent illness, etc.

4.3 **Cycle 1 (Induction)** – Patients will receive the following agents:

- Azacitidine 75 mg/m2 IV or SC (according to patient preference) on days 1-7 of each cycle
- Venetoclax 100mg on day 1, 200mg on day 2, 400mg on days 3-28
- Trametinib 2mg orally daily

Bone marrow will be performed on cycle 1 day 21 (±7 days). For patients in marrow remission (i.e. bone marrow blasts <5% or insufficient sample due to hypoplastic or aplastic marrow), venetoclax may be held at the discretion of the treating physician after discussion with the PI in order to allow for peripheral blood count recovery.

4.4 **Cycles 2-24 (Consolidation)** – Patients will receive the following agents:

- Azacitidine 75 mg/m2 IV or SC (according to patient preference) on days 1-7 of each cycle
- Venetoclax 400 mg orally daily on days 1-21
- Trametinib 2mg orally daily

4.5 Number of patients

A total of 40 patients will be enrolled (20 in each cohort). All patients on this study will be enrolled at a single site (MD Anderson Cancer Center). Patients will be considered enrolled on the day the patient is fully registered in CORE.

4.6 General Considerations

- It is strongly recommended that patients in Cohort A remain hospitalized until day 28 of cycle 1 or the time of ANC > 500, whichever occurs first. Subsequent cycles may be given as an outpatient.
- Venetoclax should be administered with food
- Trametinib should be administered on an empty stomach (1 hour before or 2 hours after a meal)
- Prevention of infection
    - Prophylactic antibiotics may be given with each course until neutrophil recovery to 500/μL or greater
    - Suggestions include: Levaquin 500 mg orally daily (or other appropriate antibacterial agent); caspofungin or other appropriate antifungal agent; valacyclovir 500 mg orally daily or acyclovir 400 mg orally twice daily or other appropriate antiviral agent.
- Azacitidine administration
    - Azacitidine may be given on days 5-2-2 which is 5 consecutive weekdays (Days 1-5) with rest on the 2 weekend days (Days 6 and 7) and then dosing the first two weekdays of the next week (Days 8 and 9) of each 28-day cycle as determined by treating physician. Azacitidine may be administered by MDACC or local physician, inclusive of regional care centers. Commercial supplies and institutional standards for administration of azacitidine will be used and records will be obtained from the local physician.
    - Both subcutaneous and IV forms of azacitidine administration are FDA-approved and are considered interchangeable, and route will be based on patient and physician preference.
    - Azacitidine administration and premedications will be per institutional standards.
- As venetoclax and trametinib are obtained commercially, some patients may have delays in beginning either agent due to financial or other logistical considerations. Even if one or both of these agents is not yet available, patients may begin azacitidine on day 1. Venetoclax and trametinib should be started when it is obtained and continued as above. To make up for missed initial doses of venetoclax, the venetoclax course may be extended up through day 28 of the cycle, although the patient may not take more than the total number of intended days of venetoclax. Failure to begin venetoclax or trametinib on day 1 will not be considered a protocol deviation.
- If azacitidine, trametinib and/or venetoclax are held or discontinued due to toxicity or any other reason (see section 7), the patient may continue on study with the remaining agent(s).
- Azacitidine, trametinib, and venetoclax will be charged to the patient/insurance. If trametinib is not approved by insurance, we will obtain through patient assistance programs. Our leukemia physicians, PAs, and pharmacists have extensive experience with obtaining off-label trametinib for patients with leukemia.

- Any expired or unused drug study medications will be destroyed according to institutional policy. This will include also any leftover medication returned by the patient.
- Delays in cycles are acceptable depending on recovery for cytopenias or other side effects, logistical concerns, or patient/physician preference in the best interest of the patient.

4.7 Suggested Standard Dose Reductions/Modifications:

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. Recommendations for dose modifications are below. Variations in dose reductions or the administration of azacitidine, venetoclax or trametinib other than those suggested below are allowed in the best interest of patients. Such patients should be discussed with the principal investigator.

- Venetoclax
  - Non-hematological toxicity - If grade 3 or 4 non-hematologic toxicity is attributable to venetoclax, dose interruption of venetoclax is required. Patients who experience drug-related grade 3 non-hematological toxicity may be given a subsequent course one dose level below the previous course, but the patient must have recovered to grade ≤1 before start of the next course. If a patient requires more than 2 dose reductions for grade 3 non-hematologic toxicity, venetoclax will be discontinued. If a patient has drug-related grade 4 non-hematological toxicity, venetoclax will be discontinued. The dose of venetoclax can be decreased during a cycle, at the discretion of treating physician and PI, for chronic grade 2 non-hematological toxicity. Other dose modifications may be considered as clinically indicated with documentation and approval of the PI. The dose reduction guidelines for venetoclax are in the table below:

Current Venetoclax Dose	**Reduced Dose**
400mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg
20mg	Hold venetoclax

Alternatively, at the discretion of the treating physician, the duration of venetoclax administration can be decreased (e.g. decrease from 21-day to 14-day administration) rather the dose being reduced. This may be performed due previous toxicity or concern for future myelosuppression or toxicity. Such modifications should be discussed with the PI and documented in the medical record.

In addition to above suggested dosing levels, venetoclax dosing may be interrupted during the course of treatment for tolerance/toxicity concerns in the judgement of the treating physician. Missed doses do not need to be made up.

- Hematologic toxicity
  - Dose interruptions or modifications will be made for grade 4 hematological toxicities only if PI strongly feel that the cytopenias are related to venetoclax and not related to underlying disease or the use of other agents. Patients with baseline neutropenia or those who have significant bone marrow involvement may be particularly at high risk.
  - If a subject achieves CRi or has a morphologically leukemia free bone marrow after completion a cycle, venetoclax may be interrupted for up to 14 days after the last day of the cycle or until recovery of ANC >500/μL.
  - If a subject presents with new onset grade 4 neutropenia for more than 1 week during subsequent cycles, unless it is thought to be due to the underlying disease, venetoclax dosing may be interrupted until ANC recovery to >500/μL in consultation with the study PI. Venetoclax may be re-initiated at a lower dose per discussion between the treating physician and the study PI. The dose reduction guidelines for venetoclax are in the table above (same as for non-hematologic toxicity).

- Azacitidine
  - Cytopenias are common in the patient population studied in this trial. Dose modification for azacitidine for grade 3-4 hematologic toxicities will be considered only if the PI strongly feel that the cytopenias were related to azacitidine and after appropriate dose reductions of venetoclax have been made, as above.

Current Azacitidine Dose	**Reduced Dose**
75mg/m2	50mg/m2
50mg/m2	37.5mg/m2
37.5mg/m2	Hold azacitidine

  - Further reductions beyond what is shown in the table above or alternative reductions (e.g. 75mg/m2 x 5 days) may be allowed if recommended by the treating physician and after discussion with the PI.
  - If the reduced dose is well tolerated and the toxicity leading to dose reduction was ≤Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle
  - If unexplained reductions in serum bicarbonate < 20 mEq/L or elevations of BUN or serum creatinine occur, consider reducing or holding the dose of azacitidine
  - If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration.

- Trametinib
  - Cytopenias are common in the patient population studied in this trial. Dose modification for trametinib for grade 3-4 hematologic toxicities will be considered only if the PI strongly feel that the cytopenias were related to trametinib and after appropriate dose reductions of azacitidine and/or venetoclax have been made, as above.
  - The following table provides dose reduction guidelines for trametinib

Current Trametinib Dose	Reduced Dose
2mg	1.5mg
1.5mg	1mg
1mg	Hold trametinib

- Cutaneous
  - Grade 2: Reduce dose level
  - Grade 2 that does not improve within 3 weeks after dose reduction or Grade 3-4: Hold trametinib for up to 3 weeks. If improved, then reduce dose
  - Intolerable Grade 2 or Grade 3-4 that does not improve within 3 weeks after dose reduction: Discontinue trametinib
- Cardiac
  - Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value: Hold trametinib for up to 4 weeks
  - Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below LLN that improves to normal LVEF value within 4 weeks following interruption: If improved within 4 weeks, then reduce dose
  - Symptomatic congestive heart failure or absolute decrease in LVEF of greater than 20% from baseline that is below LLN or absolute decrease in LVEF of 10% or greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption: Discontinue trametinib
- Ocular
  - Retinal pigment epithelial detachments (RPED): Hold trametinib for up to 3 weeks.
    - If improves within 3 weeks, then resume with same or reduced dose
    - If does not resolve within 3 weeks, then reduce dose or permanently discontinue
  - Retinal vein occlusion: Discontinue trametinib
- Interstitial lung disease/pneumonitis: Discontinue trametinib
- Other non-hematological toxicity possibly or probably related to trametinib (e.g. diarrhea)
  - Grade 3: Hold trametinib for up to 3 weeks
  - If Grade 3 adverse reaction improves to Grade 0-1 following interruption within 3 weeks: Reduce dose
  - Grade 4 adverse reaction or Grade 3 adverse reaction that does not improve to Grade 0-1 within 3 weeks: Discontinue trametinib

4.8 Prophylaxis and Management of TLS

- There is a potential for TLS, especially in those with elevated pretreatment LDH levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk for

TLS, subjects will receive tumor lysis prophylaxis, including hydration (e.g., oral, intravenous) and treatment with an agent to reduce the uric acid level (e.g., allopurinol, rasburicase) prior to and during at least the first 1 week of cycle 1. For subjects who had dose delay or interruptions, TLS prophylactic measures may need to be implemented based on the disease status prior to resuming treatment. TLS prophylaxis must be initiated in all such subjects prior to the first venetoclax dose or first new escalated dose.

- In cycle 1 during venetoclax dose-escalation, TLS chemistry tests (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) should be checked on the first day of venetoclax and each day of a new dose prior to venetoclax dosing. TLS chemistry tests should also be checked approximately between 4-12 hours after each new dose of venetoclax (i.e. during the venetoclax ramp-up).

4.9 Definition of DLT

A DLT will be defined as any of the following adverse events that cannot be considered primarily related to the underlying malignancy, a comorbid condition, or a concomitant medication, occurring between day 1 and day 28 of cycle 1 (with the exception of hematologic toxicity which may be assessed up to day 42 of cycle 1)

Any ≥ grade 3 non-hematologic toxicity with the following exceptions:

- Grade 3 alopecia
- Grade 3 nausea, vomiting, diarrhea with electrolyte abnormalities lasting less than 48 hours that are not clinically significant and that does not require total parenteral nutrition (TPN), tube-feeding, or hospitalization
- Grade 3 or 4 liver abnormalities (AST, ALT, or alkaline phosphatase) that resolve to < grade 2 within 5 days
- Grade 3 hyperbilrubinemia that resolves to < grade 2 within 5 days
- Grade 3 indirect hyperbilirubinemia
- Infection, unless the infection resulted from unexpectedly complicated by the degree or duration of myelosuppression in the absence of persistent leukemia.

Patients who receive at least a full course of therapy will be considered to be evaluable for toxicity/DLT and will not be replaced unless the PI determines that further additional patients at that dose level are required for safety purposes.

For patients who do not receive venetoclax and/or trametinib on day 1 of cycle 1 due to logistical and/or financial reasons, the DLT period will be extended to 28 days from the first dose of venetoclax and/or trametinib (whichever starts later). For evaluation of neutropenia-related DLT, the DLT period will be 42 days from the first dose of venetoclax and/or trametinib (which ever starts later).

Hematologic toxicity will be defined as failure to recover ANC > 500/μL or platelet count > 25,000/μL by day 42. This will be considered DLT. However, for patients with $\underline{\geq}$ 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover neutrophil or platelet count will not be considered a DLT as this could be the result of persistent disease.

5. CONCOMITANT MEDICATIONS

- Concomitant medications will be documented in the subject's electronic medical record.
- G-CSF is allowed if needed to hasten count recovery at the discretion of the treating physician
- Use of hydroxyurea during the study may be permitted as clinically indicated, on a case-by-case basis and after discussion with the PI
- Intrathecal chemotherapy for prophylaxis or treatment of known or suspected CNS disease may be permitted as clinically indicated, on a case-by-case basis and after discussion with the PI
- Patients may be concurrently enrolling in supportive care clinical trials with exclusion medications that listed below. Other investigational agents that are used for treatment of other cancers will not be allowed.
- Strong CYP3A or p-glycoprotein inducers are not permitted while on study. These agents include but at not limited to: carbamazepine, phenytoin, rifampin and St. John's wart.
- Moderate CYP3A inducers and moderate or strong CYP3A inhibitors are discouraged while on study. If a patient requires use of moderate CYP3A inducers, use with caution. In many instances, such as antifungal prophylaxis with "azole" therapy in neutropenic patients, CYP3A inhibitors are required in AML patients. Venetoclax should be administered at 50% dose reduction in the setting of moderate CYP3A inhibitors (i.e. isavuconazole, ciprofloxacin, diltiazem) and 75% dose reduction with strong CYP3A inhibitors (e.g. voriconazole), with the exception of posaconazole in which an ~83% dose reduction should be used (i.e. 70mg with posaconazole). The venetoclax dose reduction should continue for the duration of co-administration. In the event the co-administered CYP3A inhibitor is discontinued, the assigned venetoclax dose should be resumed 2-3 days after discontinuation. During the venetoclax ramp-up, these agents must be held; however, they may be started or resumed 24-72 hours after the highest planned dose of venetoclax is given, along with the appropriate dose reduction of venetoclax as above. No dose reductions will be performed for azacitidine or trametinib based on concomitant medications.

  Drugs involving these enzymes and transporters can be found in the following webpage: http://medicine.iupui.edu/clinpharm/ddis/main-table/

6. STUDY PROCEDURES

6.1. Pre-Treatment Evaluation

1. History and physical examination, including vital signs, height, weight, and performance status
2. CBC with differential, electrolytes (potassium, calcium, magnesium, bicarbonate, phosphorus), LDH, uric acid, creatinine, liver function tests (AST and/or ALT and total bilirubin). *Differential does not need to be performed if white blood cell count is <0.4 K/μL.*
3. Bone marrow aspirate, cytogenetics, 81-gene mutation panel (or similar mutation screen) must have be sent within 4 weeks of enrollment.
4. Peripheral blood and bone marrow samples for correlative studies

5. Pregnancy test in female patients of appropriate age and menopausal state within 1 week of first dose
6. Echocardiogram or MUGA scan to assess cardiac function within 4 weeks of first dose

All pretreatment evaluation must be performed within 2 weeks of first dose of the study drug, unless otherwise specified as above.

6.2 Evaluation During Study

1. History and physical examination, including vital signs and weight prior to each cycle
2. Evaluation for toxicity assessment prior to each cycle
3. Assessment of concomitant medications prior to each cycle
4. In addition to TLS monitoring during the venetoclax ramp-up period (section 4.8), CBC with differential, electrolytes (potassium, calcium, magnesium, bicarbonate, phosphorus), LDH, uric acid, creatinine, liver function tests (AST and/or ALT and total bilirubin) at least 1-2 times per week during cycle 1, then prior to each subsequent cycle. *Differential does not need to be performed if white blood cell count is <0.4 K/µL.*
5. Echocardiogram or MUGA scan to assess cardiac function every 2-3 months (for patients still on trametinib)
6. Bone marrow aspiration (including flow cytometry for MRD, and cytogenetics [for patients in whom last bone marrow had abnormal cytogenetics]) to be performed at a minimum on:
    a. Cycle 1 day 21 (±7 days) – For patients in marrow remission on the Cycle 1 day 21 bone marrow (i.e. bone marrow blasts <5% or insufficient sample due to hypoplastic or aplastic marrow), venetoclax may be held at the discretion of the treating physician after discussion with the PI in order to allow for peripheral blood count recovery.
    b. Cycle 1 day 28 (±7 days) – will be performed at least 7 days after C1D21 (± 7 days) if marrow remission is not achieved.
    c. Cycle 2 day 28 (±7 days) – only required for patients who did not achieve CR/CRi at end of cycle 1
    d. Cycle 4 day 28 (±7 days)

    During bone marrows at end of cycles 1, 2, and 4 and at the time of relapse, additional aspirate will be collected for correlative studies, including single-cell sequencing. After the end of cycle 4 bone marrow, additional bone marrow assessments should be performed every 2-4 cycles or as clinically indicated.

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycles 4+	End of Treatment	Follow-Up
Informed consent	X						
History + physical	X						
Vital signs	X	X	X	X	Every cycle		
Performance Status	X						
Concomitant medication and AE assessment	X	X	X	X	Every cycle		
Toxicity assessment		X	X	X	Every cycle	X	X
CBC with diff	X	X	X	X	Every cycle		
Electrolytes (potassium, calcium, magnesium, bicarbonate phosphorus), LDH, uric acid, creatinine, liver function tests (AST or ALT, total bilirubin)	X	X	X	X	Every cycle		
Bone marrow aspirate	X	X	X[1]		X[2]		

Pregnancy test (If indicated)	X						
Echocardiogram or MUGA[3]	X						
Peripheral blood for correlative studies	X						

[1] Only required for patients who did not achieve CR/CRi at end of cycle 1
[2] Every 2-4 cycles or as clinically indicated
[3] Repeat every 2-3 months while on therapy (for patients still on trametinib)

Failure to obtain samples for correlative work (e.g. single-cell sequencing) during either the pre-treatment evaluation or during study will not result in a protocol deviation.

6.3 End of treatment visit

At the time of withdrawal, the following study procedures visit should be completed:

1. Evaluation for toxicity assessment

6.4 Follow-up

Thirty days after last dose of the study drugs toxicity assessment will be recorded. This may be done over the phone with a member of the study staff.

6.5 Long-Term Follow-up

After discontinuing study treatment (unless discontinuing due to withdrawal of consent) patients will be followed for disease progression, relapse, and survival. Patients will be followed for survival every 6 months (±3 months) until death via brief phone call, even after being taken off treatment. For patients registered on our long-term follow-up umbrella protocol DR09-0223, survival follow-up may be conducted under that protocol.

7. EFFICACY AND SAFETY ASSESSMENTS

7.1. CRITERIA FOR RESPONSE

Response assessment will be conducted by the PI using standard criteria [15] and recorded in the patient's electronic medical record.

1. Response Criteria for AML:
    a. Complete Remission (CR): Normalization of the peripheral blood and bone marrow with 5% or less blasts in normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above, and platelet count of 100 x 10^9/L. Complete resolution of all sites of extramedullary disease is required for CR.
    b. CR without minimal residual disease (CR_{MRD-}) = CR with negativity by multi-color flow cytometry.
    c. Complete remission without recovery of counts (CRi): Peripheral blood and marrow results as for CR, but with incomplete recover of counts (platelets < 100 x 10^9/L or neutrophils < 1 x 10^9/L).
    d. Morphologic leukemia-free state (MLFS) = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required. At least 200 cells should be enumerated or cellularity of the bone marrow should be at least 10%.

e. Partial remission (PR) = All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% - 25%, and decrease of pretreatment bone marrow blast percentage by ≥50%.
f. Stable disease (SD) = Absence of CRMRD-, CR, CRi, PR, MLFS; and criteria for PD not met.
g. Progressive disease (PD) = Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast count in the blood:
    i. >50% increase in marrow blasts (must be confirmed by repeat marrow examination ≥4 weeks later) over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over ≥3 months; without at least a 100% improvement in ANC to an absolute level of >0.5 x 10^9/L [500/μL], and/or platelet count to >50 x 10^9/L [50,000/μL] non-transfused); or
    ii. >50% increase in peripheral blasts to >25 x 10^9/L (25,000/μL) in the absence of differentiation syndrome; or
    iii. New extramedullary disease.
h. Hematologic relapse (after CRMRD-, CR or CRi) = Bone marrow blasts ≥5% or appearance of blasts in the blood, or development of extramedullary disease.
i. Molecular relapse (after CR_{MRD-}) = Recurrence of MRD by flow cytometry.
j. The following types of response or treatment failure will be recorded in medical record CR (CR, CR-MRD, or CRi) or what type of treatment failure (SD, PD, hematologic relapse or molecular relapse) they had.
    i. Complete Remission (CR, CR-MRD, or CRi)
    ii. Treatment Failure (stable disease, progression or relapse)
    iii. Inevaluable
    iv. Not Applicable (N/A)

2. For patients with MDS or CMML, the response criteria from the International Working Group as summarized in Cheson BD et al. *Blood* 2006;108(2):419-25 will be used.

7.2. EVALUATION OF TOXICITY

1. Toxicities will be graded according to the NCI Common Toxicity Criteria for Adverse Event Reporting Version 5.0. The toxicity of the regimen will be monitored continuously during the course of the study.

7.3. CRITERIA TO STOP TREATMENT

1. Failure to achieve CR/CRi/MLFS after 6 cycles of treatment, unless the patient is deemed to be deriving clinical benefit (e.g. blast reduction not meeting criteria for CR/CRi/MLFS) as assessed by the treating physician and PI
2. Unacceptable toxicity judged to be related to therapy by the investigator, as defined by the NCI Common Toxicity Criteria (irreversible or prolonged (> 42 days) grade 4 hematological toxicity or grade 4 non-hematological toxicity thought to be related to azacitidine, trametinib or venetoclax), unless it has been judged by the treating physician and PI that the patient is achieving clinical benefit.
3. Pattern of non-compliance by the patient with protocol requirements or patient's request to be removed from the study.
4. Relapse, defined as >5% bone marrow blasts not attributed to hematopoietic recovery, occurring after initial response to therapy
5. At the discretion of the treating physician and/or PI

Patients coming off treatment due to the above issues will continue to be followed for survival outcomes.

7.4 DEFINITION OF STUDY ENDPOINTS

1. **Relapse-free survival** is the time from documented CR/CRi until relapse or death.

2. **Event-free survival** is the time from the first day of treatment until any treatment failure (lack of response within 6 cycles of treatment, relapse, or death).

3. **Overall response rate** is defined as the percentage of patients achieving CR or CRi.

4. **Overall survival** is defined as the time from the first day of treatment to time of death from any cause.

In the primary analysis, survival will not be censored for stem cell transplant.

8. REPORTING REQUIREMENTS

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines (refer to appendix E).

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, and Institutional Review Board (IRB) policy.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50).

9. OUTSIDE PHYSICIAN PARTICIPATION DURING TREATMENT

9.1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.

9.2 A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care

9.3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be reviewed by the MDACC physician and any additional medical intervention is required it will be documented within the patient's medical record

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

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

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

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

9.8 For non MD Anderson laboratory results, the principal investigator (or physician designee) will review laboratory results, determine clinical significance, and sign and date the results.

10. STATISTICAL METHODOLOGY

This is an open label, phase II study with a lead-in phase to assess the MTD and the efficacy of the combination regimen of azacitidine, venetoclax, and trametinib in patients with AML or MDS/CMML. A total of 40 patients will be enrolled for the study: 20 patients with newly diagnosed AML (Cohort A) and 20 patients with relapsed/refractory AML or higher-risk MDS or CMML (Cohort B).

In order to confirm the safety of azacitidine, venetoclax, and trametinib, there will be a lead-in phase for the regimen safety. The regimen will initially be explored in 6 eligible patients meeting criteria for enrollment in Cohort B (i.e. relapsed/refractory). If none or only one of the 6 patients experiences DLT in first cycle attributable to the treatment components, the phase II portion of the study will proceed as detailed below. The patients treated in this confirmatory phase will be counted towards the phase II component of the study. If DLT attributable to the components is observed in 2 or more of these initial 6 patients, accrual to the phase II portion of the study will be deferred, and a lower dose of the combined agents would be assessed based on the investigators' decision, which will be implemented with amendment to the study.

Cohort A:

The historical 1-year overall survival rate (OSR) for newly diagnosed patients is 59% and for this cohort the target OSR is 65% for the experimental treatment. A >30% clinically significant drug-related grade 3 or higher toxicity rate occurred in the 1st cycle is considered unacceptable. A sample size of 20 patients ensures that, if the cohort is not terminated early, a posterior 95% credible interval for OSR will be (0.38, 0.78) under the assumption of a 59% of OSR and prior Beta (1.18, 0.82). Thus, interim monitoring rules, assuming the prior distributions below, were constructed that meet the following two conditions,

1) Stop if Prob[$p(OSR, H) + \delta_{OSR} > P(OSR, E) \mid data] > 0.95$, where $\delta_{OSR} = 0.06$ or
2) Stop if Prob[$p(TOX,H) + \delta_{TOX} < p(TOX,E) \mid data] > 0.90$, where $\delta_{TOX} = 0$,

where p(OSR, H) and p(OSR, E) are the true OSR for the historical and experimental treatments, respectively. The p(TOX, H), and p(TOX, E) are the toxicity rates for the historical and experimental treatments, respectively. The first rule provides for stopping the study if the data suggest that it is unlikely (i.e., probability < 5%) that OSR rate of the regimen is greater than 65%. The second condition will stop the study early if excessive therapy-related grade 3 or higher toxicity (>30%) is highly probable (i.e., probability >90%) for the combination treatment. Monitoring for toxicity and futility will not begin until 4 patients have been evaluated, and cohort size for future evaluations is 4.
The monitoring rule for the toxicity and OSR rates, based on these assumptions and monitoring conditions above is found in Table 1. For example, accrual will cease if 3 or more patients experience toxicities among the first 4 patients. Accrual will cease if none of first 4 patients treated are alive.

Table 1. Stopping boundary for efficacy and toxicity

# patients evaluated	Stop the cohort if there are this number of patients	
	# alive	with toxicities
4	0	3-4
8	0-2	5-8
12	0-4	6-12
16	0-7	8-16
20	Stop due to maximum sample size	Stop due to maximum sample size

Table 2 shows the operating characteristics for simultaneous monitoring response and toxicity rates. The probability of stopping the study early if the true OSR rate of the combination treatment was 65% and the true toxicity rate was 30% was 25%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 74% when the true OSR was 65%.

Table 2. Operating characteristics for simultaneous monitoring response and toxicity rates

True Toxicity Rate	True OSR	Prob(stop the cohort early)
0.20	0.55	0.3163
	0.60	0.2037
	0.65	0.1255
	0.70	0.0793
	0.75	0.0566
0.30	0.55	0.4135
	0.60	0.3169
	0.65	**0.2498**
	0.70	0.2102
	0.75	0.1907
0.40	0.55	0.5940
	0.60	0.5271
	0.65	0.4806
	0.70	0.4532
	0.75	0.4397
0.50	0.55	0.7956

Table 2. Operating characteristics for simultaneous monitoring response and toxicity rates		
True Toxicity Rate	True OSR	Prob(stop the cohort early)
	0.60	0.7619
	0.65	0.7386
	0.70	0.7247
	0.75	0.7179

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the operating characteristics table. In order to utilize the software for the design, a 59% constant rate, a 6% delta and beta (1.18, 0.82) priors were assumed for the standard treatment response rate and experimental treatment response prior distribution, respectively. In addition, a 30% constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity rate and experimental treatment toxicity prior distribution, respectively.

Cohort B:

The target CR/CRi/MLFS rate is 35% evaluated within 6 cycles of treatment. A >30% clinically significant drug-related grade 3 or higher toxicity rate occurred in the 1st cycle is considered unacceptable. A sample size of 20 patients ensures that, if the cohort is not terminated early, a posterior 95% credible interval for CR/CRi/MLFS will be (0.17, 0.56) under the assumption of a 35% of CR/CRi/MLFS and prior Beta (0.7, 1.3). Thus, interim monitoring rules, assuming the prior distributions below, were constructed that meet the following two conditions,

1) Stop if Prob[p(CR/CRi, E) < 0.35 | data] > 0.95, or
2) Stop if Prob[p(TOX, E) > 0.30 | data] >0.93,

where p(CR/CRi/MLFS, E) and p(TOX, E) are the true CR/CRi/MLFS and toxicity rates for the regimen. The first rule provides for stopping the study if the data suggest that it is unlikely (i.e., probability < 5%) that CR/CRi/MLFS rate of the regimen is greater than 35%. The second condition will stop the study early if excessive therapy-related grade 3 or higher toxicity (>30%) is highly probable (i.e., probability >93%) for the combination treatment. Monitoring for toxicity and futility will not begin until 4 patients have been evaluated, and cohort size for future evaluations is 4.

The monitoring rule for the toxicity and CR/CRi/MLFS rates, based on these assumptions and monitoring conditions above is found in Table 3. For example, accrual will cease if 3 or more patients experience toxicities among the first 4 patients. Accrual will cease if no patient experience an overall response in the first 8 patients treated.

Table 3. stopping boundary for efficacy and toxicity		
# patients evaluated	Stop the cohort if there are this number of patients	
	# patients with CR/CRi/MLFS	# patients with toxicities
4	Never stop	3-4
8	0	5-8

12	0-1	7-12
16	0-2	8-16
20	Stop due to maximum sample size	Stop due to maximum sample size

Table 4 shows the operating characteristics for simultaneous monitoring response and toxicity rates. The probability of stopping the study early if the true CR/CRi/MLFS of the combination treatment was 35% and the true toxicity rate was 30% was 21%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 75% when the true CR/CRi/MLFS was 35%.

Table 4. Operating characteristics for simultaneous monitoring response and toxicity rates

True Toxicity Rate	True CR/CRi/MLFS	Prob(stop the cohort early)
0.20	0.25	0.2785
	0.30	0.1728
	0.35	0.1076
	0.40	0.0709
	0.45	0.0519
0.30	0.25	0.3628
	0.30	0.2694
	0.35	**0.2118**
	0.40	0.1794
	0.45	0.1626
0.40	0.25	0.5372
	0.30	0.4695
	0.35	0.4276
	0.40	0.4041
	0.45	0.3919
0.50	0.25	0.7544
	0.30	0.7184
	0.35	0.6962
	0.40	0.6837
	0.45	0.6772

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the operating characteristics table. In order to utilize the software for the design, a 35% constant rate and beta (0.7, 1.3) priors were assumed for the standard treatment response rate and experimental treatment response prior distribution, respectively. In addition, a 30% constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity rate and experimental treatment toxicity prior distribution, respectively.

Analysis Plan: Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range.

For the primary efficacy analysis, we will estimate the CR/CRi/MLFS for the combination treatment (defined as the proportion of patients achieving CR or CRi or MLFS within 6 cycles of treatment), along with the 95% credible interval. This regimen will be considered worthy of further investigation if a CR/CRi/MLFS rate of at least 35% is achieved for frontline patients (Cohort B). Other efficacy endpoints (e.g. CR rate, CR/CRi rate, minimal residual disease negativity, or proportion of patients proceeding to HSCT) will also be estimated along with 95% credible intervals. The association between response and patient's clinical characteristics (e.g., baseline apoptotic protein levels, baseline FLT3 allelic ratio, or baseline genomic alterations) will be examined by Wilcoxon's rank sum test or Fisher's exact test, as appropriate.

For each subject, relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS) will be calculated. The distribution of time-to-event endpoints (OS, EFS and OS) will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups (e.g., baseline genomic alterations will be made using the log-rank tests.

11. DATA CONFIDENTIALITY

Epic is the source for all patient data. Patient data will be extracted from Epic to Department Database (MOCLIA). This secure database resides in the MDACC IT environment and is an institutionally approved database for use as described in this protocol.

12. PROTOCOL MONITORING

This protocol will be monitored by the MD Anderson Data Safety Monitoring Committee (DSMC).

13. REFERENCES

1. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126:291-9.
2. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:2670-7.
3. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. The Lancet Oncology 2018;19:216-28.
4. DiNardo CD, Pollyea DA, Jonas BA, et al. Updated Safety and Efficacy of Venetoclax with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia. Blood 2017;130:2628-.
5. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. American journal of hematology 2018;93:401-7.
6. Aldoss I, Yang D, Aribi A, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. Haematologica 2018.
7. Goldberg AD, Horvat TZ, Hsu M, et al. Venetoclax Combined with Either a Hypomethylating Agent or Low-Dose Cytarabine Shows Activity in Relapsed and Refractory Myeloid Malignancies. Blood 2017;130:1353-.
8. Short NJ, Ravandi F. Acute Myeloid Leukemia: Past, Present, and Prospects for the Future. Clinical lymphoma, myeloma & leukemia 2016;16 Suppl:S25-9.
9. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. Lancet 2018;392:593-606.

10. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133:7-17.
11. Chyla B, Daver N, Doyle K, et al. Genetic Biomarkers Of Sensitivity and Resistance to Venetoclax Monotherapy in Patients With Relapsed Acute Myeloid Leukemia. American journal of hematology 2018.
12. Han L, Zhang Q, Dail M, et al. Concomitant targeting of BCL2 with venetoclax and MAPK signaling with cobimetinib in acute myeloid leukemia models. Haematologica 2019.
13. Borthakur G, Popplewell L, Boyiadzis M, et al. Activity of the oral mitogen-activated protein kinase kinase inhibitor trametinib in RAS-mutant relapsed or refractory myeloid malignancies. Cancer 2016;122:1871-9.
14. DiNardo CD, Tiong IS, Quaglieri A, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. Blood 2020;135:791-803.
15. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2016.