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Integrating Geriatric Assessment and Genetic Profiling to Personalize Therapy Selection in Older Adults with Acute Myeloid

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INTEGRATING GERIATRIC ASSESSMENT AND GENETIC PROFILING TO PERSONALIZE THERAPY SELECTION IN OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA

by

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ABSTRACT

Integrating geriatric assessment for patient profiling and genetic profiling of leukemic cells represents an innovative approach to personalize therapy selection in older adults with acute myeloid leukemia (AML). We report results of a pre-planned interim analysis of a pragmatic phase II trial that utilized this strategy to personalize therapy. Patients ≥60 years with a new diagnosis of AML underwent geriatric assessment prior to initiation of treatment. Geriatric assessment of physical function, cognitive function and comorbidity burden were used to determine fitness for chemotherapy. Patients with good or intermediate-risk AML received intensive chemotherapy such as anthracycline and cytarabine (7+3) if determined to be fit. Patients with high-risk AML received low-intensity chemotherapy, or liposomal preparation of anthracycline and cytarabine (CPX 351) if they met the FDA approved indication and were fit. The pre-planned interim analysis results are based on the first 27 AML patients. Characteristics included a median age of 70 years (range 60-84 years), 56% female, and 96% white. Over half of the patients had ≥3 comorbidities, impairment in objective physical function or cognitive screen. Risk categories included adverse (64%), intermediate (16%), and good-risk AML (20%) (2017 European LeukemiaNet criteria). Three patients received intensive chemotherapy; other received low intensity chemotherapy. The median time from enrollment to treatment initiation was 2 days (range 0-9). Mortality at 30 days was 3.7% and at 90 days was 29.6%. In conclusion, our

study results demonstrate feasibility of using geriatric assessment and genetic profiling of leukemia cells to personalize therapy selection in older adults with AML.

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LIST OF ABBREVIATIONS

7+3 7-day cytarabine and 3-day anthracycline

ADL Activities of Daily Living

AML Acute Myeloid Leukemia

AML MRC Acute Myeloid Leukemia with Myelodysplasia-Related Changes

BMI Body Mass Index

CBC Complete Blood Count

CI Confidence Interval

CMP Comprehensive Metabolic Panel

ELN European LeukemiaNet

EORTC QLQ C-30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30

FDA Food and Drug Administration

IADL Instrumental activities of daily living

KPS Karnofsky Performance Status

LDAC Low-Dose Ara-C or Low-Dose Cytarabine

MOCA Montreal Cognitive Assessment

MUGA scan multigated acquisition scan

NCCN National Comprehensive Cancer Network

WHO World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is among the most common hematologic malignancies in adults and is commonly diagnosed in the sixth or seventh decades of life [1]. AML accounts for approximately 10,000 deaths in the United States every year [2]. In patients with AML, the myeloblasts proliferate in bone marrow and replaces normal hematopoietic cells. This results in development of anemia, thrombocytopenia, and neutropenia. Patients present with fatigue, bruises, shortness of breath, weight loss, and fever. Patients are at risk of serious infection, bleeding, and complications as a result of excess quantity of white blood cells or hyperleukocytosis. A bone marrow biopsy demonstrating more than 20% blasts can confirm the diagnosis. Patients with AML are categorized into good, intermediate and high-risk AML based on cytogenetic criteria put forth by the 2017 European LeukemiaNet (ELN) criteria.[3]

1.2 Management of AML in Older Adults

The management of AML is complex in older patients because of associated comorbidities, intolerance to high-dose chemotherapy, and high-risk tumor biology. For example, in real world practice, over half of patients aged 60 years and older do not receive initial chemotherapy for AML. Consequent to such complexities of AML in older patients and current practice patterns, only 10-20% of patients are alive at 3-5 years in the real world [4-6]. Survival has not improved significantly in the last few decades. Poor survival of older patients with AML may be improved with refined risk-stratification and therapy selection strategies, integration of principles of geriatric medicine, and use of effective but low intensity and novel therapies.

Previously, treatment options for patients with AML included a combination of 7-day cytarabine and 3-day anthracycline (so-called “7+3”), and hypomethylating agents such as azacytidine or decitabine. In 2017, the Food and Drug Administration (FDA) approved gemtuzumab ozogamicin (a humanized CD-33 directed monoclonal antibody-drug conjugate), CPX-351 (liposomal preparation of anthracycline and cytarabine), and midostaurin (FLT3 inhibitor in patients with FLT3 mutated AML) in initial management of AML. Gemtuzumab ozogamicin is approved for CD-33 positive AML (blasts from AML patients are generally CD33 positive); however, the survival benefit with its’ use is the highest among patients with good or intermediate risk AML [7]. CPX-351[8, 9] is FDA-approved (because of survival benefit over 7+3) for patients with prior exposure to chemotherapy or radiation, or those with certain genetic markers (AML with myelodysplasia-related changes, as defined by WHO.[10] The addition of the FLT3 inhibitor midostaurin [11] in FLT3 mutated patients is also associated with a survival benefit; this has been specifically demonstrated in a phase 3 trial for younger adults. In 2018, the FDA approved venetoclax (inhibits the anti-apoptotic protein BCL-2) and glasdegib (small molecule inhibitor of the Hedgehog pathway) for AML. Venetoclax is approved in combination with low-dose cytarabine (LDAC) or hypomethylating agents, decitabine or azacitidine.[12-14] Glasdegib is approved in combination with LDAC.[15]

1.3 Value of individualized therapy selection

In older patients with AML, practical and rational therapy selection is crucial to deliver chemotherapy that is most likely to benefit an individual patient. Select patients are able to tolerate intensive therapy, and achieve high rates of complete remission and long-term survival.[16, 17] Such patients are likely to benefit from intensive chemotherapy. Conversely, most older patients have significant comorbidities requiring multiple

medications, cognitive impairment, or malnutrition, and are not physically fit to reap the benefit of intensive chemotherapy.[18-21] The use of intensive chemotherapy in such patients may result in significant toxicities, poor quality of life, deterioration in physical and neurocognitive status, and high early mortality rates.[22] Such patients are better served with low intensity chemotherapy rather than intensive chemotherapy. Hence, individualized therapy selection should balance both anticipated benefits and risks of toxicities.

1.4 Current therapy selection strategies

The current approach for therapy selection is largely subjective based on chronological age, performance status and/or comorbidities, and does not clearly identify patients who should undergo or forego intensive chemotherapy.[23, 24] Additionally, for most older patients, except for those with good-risk cytogenetic markers, the goal of initial chemotherapy should be to allow eligible patients to undergo allogeneic hematopoietic cell transplant because transplant, compared to chemotherapy alone, offers a significantly higher possibility of long-term disease control in high-risk patients.[25] The benefit of transplant is higher in patients who achieve complete remission without significant decline in functional status. The use of intensive chemotherapy in older patients may be associated with a risk of functional decline and toxicities that may preclude the safe use of allogeneic transplant.[26, 27] Until recently, low intensity chemotherapy options resulted in low rates of complete remission and a small probability of undergoing allogeneic transplantation. However, this has changed with the approval of several novel low-intensity agents. The outcomes of older patients with high-risk AML can improve with enhanced risk-stratification and therapy selection strategies, and with

the use of low intensity but effective chemotherapy in patients who are not fit to receive intensive chemotherapy.

1.5 Integration of geriatric assessment

Comprehensive geriatric assessment offers a thorough assessment of multiple health domains including comorbidities, polypharmacy, cognitive, nutritional, psychological, functional, and social status. Such multidimensional assessment based on geriatric principles is an important tool that can improve risk-stratification and therapy selection in older patients. This approach provides a deeper understanding of the biological age and physical fitness of patients, and anticipated tolerance to chemotherapy. In older patients with AML, previous studies have demonstrated that comprehensive geriatric assessment is feasible,[18] uncovers significant functional impairments[18] and predicts toxicities and overall survival.[19-21] Hence, geriatric assessment is considered superior to therapy allocation based on assessment of age and performance status.[1] Recently, geriatric assessment-guided therapy allocation has been demonstrated to be feasible in older patients with lung cancer and was shown to reduce toxicities compared to therapy allocation based on age and performance status.[28] Based on these rationales, the National Comprehensive Cancer Network (NCCN) guidelines[29] recommend integrating geriatric assessment in therapeutic decision-making.

1.6 Impact of leukemia cytogenetics on outcomes

Studies in AML have clearly demonstrated the influence of leukemia cytogenetics on the probability of complete remission and survival with intensive chemotherapy.[30, 31] Good-risk AML in fit, older patients is associated with a high complete remission rate (up

to 80%[16, 17]) and survival (60% at 2 years[17] and 40% at 5 years[16]) when treated with intensive chemotherapy such as anthracycline and cytarabine, hence such patients are good candidates for intensive chemotherapy. The outcomes of older patients, who are unfit, or have high-risk AML are poor with chemotherapy alone.[32] In these patients, at best, complete remission rates are 30-60%, induction mortality is high (10-40% depending on age and performance status[22]), and long-term survival at 5 years is less than 10-20%.[16, 17] Although beneficial, allogeneic transplant is not feasible in many older patients, in part because of induction mortality and functional decline from intensive chemotherapy.[26, 27] Recently, CPX-351[8, 9] has demonstrated survival benefit over 7+3 for patients with prior exposure to chemotherapy or radiation, or those with certain genetic markers (AML with myelodysplasia-related changes, as defined by World Health Organization (WHO) [10]. For this reason, CPX-351 received FDA approval in these subsets of patients.

1.7 Study Rationale

Given the powerful impact of leukemia cytogenetics and functional status determined by geriatric assessment on outcomes, there is a rationale to integrate these multidimensional assessments into clinicogenetic risk-stratification strategy. While the cytogenetic risk category can provide a probability to achieve complete remission with chemotherapy, the findings of geriatric assessment can predict anticipated toxicity risk. Thus, a combination of clinical parameters such as level of fitness of patients as measured by geriatric assessment, and cytogenetic features of leukemia can provide a strategy to individualize therapy selection. The aim of such individualized therapy is to optimize the benefit of chemotherapy in patients most likely to benefit from intensive

chemotherapy while reducing the risk of serious toxicities because of intolerance to chemotherapy.

CHAPTER 2: METHODS

2.1Study Design

This is a phase II trial that will evaluate the impact of clinicogenetic risk-stratified management on early mortality of AML in older patients. The study schema is shown in Figure 1.

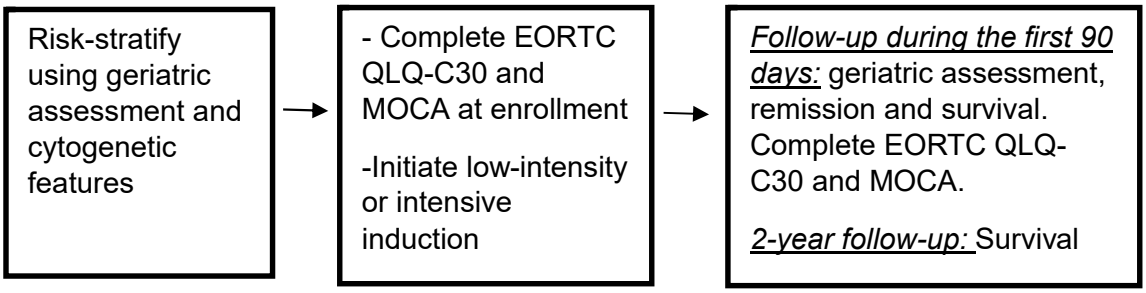

Figure 1. Risk-stratified management of older patients with AML. EORTC QLQ-C30 indicates European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30, and MOCA indicates Montreal Cognitive Assessment.

2.2 Eligibility Criteria

Study population will include eligible older patients with histologically confirmed newly diagnosed AML.

Inclusion criteria:

1. A new diagnosis of *de novo,* secondary or treatment-related AML, other AML equivalent such as myeloid sarcoma, myelodysplastic syndrome in transformation to AML, or high-grade treatment-related myeloid neoplasm
2. Patients aged ≥60 years
3. Karnofsky Performance Status ≥60%
4. Subjects must be able and willingly give signed informed consent

Exclusion criteria:

1. Acute promyelocytic leukemia (APL). Patients with brief exposure to all-trans retinoic acid (ATRA), arsenic trioxide (ATO) or similar product for suspected APL, who later turn out not to have APL, are eligible for the study.
2. Relapsed or refractory AML, who require salvage therapy
3. Prior exposure to decitabine or azacitidine will be an exclusion criterion for the use of decitabine or azacitidine alone.
4. Patients, who require urgent initiation of chemotherapy (other than debulking agent such as hydroxyurea or cyclophosphamide) due to leukemia-related emergencies such as leukostasis, or disseminated intravascular coagulopathy. Patients will not be excluded solely based on prior use of debulking agent. Prior or current use of leukapheresis will be allowed.
5. Uncontrolled serious infection at the time of enrollment. Infections are considered controlled if appropriate therapy has been instituted and, at the time of enrollment, patients do not have signs of infection progression. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection
6. Uncontrolled clinically significant arrhythmia, myocardial ischemia or congestive heart failure within the past 2 weeks, that is considered by the treating physician as a contraindication for initiation of chemotherapy. Discussion with the principal investigator is encouraged if further clarification is required.
7. Ejection fraction <45% will be an exclusion criteria for intensive chemotherapy. Such patients may receive low intensity therapy.

8. Clinically significant kidney (e.g. GFR ≤45ml/minute or Creatinine of ≥2 mg/dl) or liver dysfunction (e.g. AST/ALT and/or bilirubin ≥2 times ULN) at the time of enrollment that may prevent from safely using chemotherapy. Such patients may be allowed to receive low-intensity chemotherapy. Patients with elevated bilirubin secondary to Gilbert syndrome will not be excluded. Discussion with the principal investigator is encouraged if further clarification is required.
9. Any other condition that may not allow safe use of chemotherapy based on the clinical judgment of the treating oncologist.

2.3 Treatment Plan

This is a phase II trial for patients with AML. Eligible patients will undergo risk-stratification based on geriatric assessment and cytogenetic features. Cytogenetic analysis will be done as clinically indicated per current standard of care for management of patients with AML.

2.3.1 Comprehensive Geriatric assessment: Comprehensive geriatric assessment will include evaluation of multiple domains (Table 1).

Table 1. Summary of Comprehensive Geriatric Assessment

Domains	Instruments
Comorbidity	Hematopoietic Cell Transplantation Comorbidity Index score
Polypharmacy	Patient interview/Medical record
Nutrition	Mini Nutritional Assessment-Short Form,*
Functional status	
ADL	Katz ADL Index
IADL	Lawton IADL Index
Mobility	Short Physical Performance Battery
Social Support	Medical Outcomes Study Social Function Scale
Depression	Patient Health Questionnaire-9†
Cognition	Montreal Cognitive Assessment
Geriatric syndromes	Falls in last 6 months, history of dementia or delirium, history of urinary or stool incontinence

ADL indicates activities of daily living; IADL indicates instrumental activities of daily living.

*A score of 11 or less on Mini Nutritional Assessment is considered abnormal.

†A score of 10 or higher on Patient Health Questionnaire-9 is indicative of major depression.

Comorbidity: Comorbidity burden will be calculated according to the Hematopoietic Cell Transplantation Comorbidity Index score.[33] It predicts treatment-related mortality and is more sensitive than the Charlson Comorbidity Index in older adults with AML.[34] CPX-351 has shown to improve survival over 7+3 among patients who develop AML following use of chemotherapy or radiation for prior malignancies. Patients treated with CPX-351 are more likely to undergo curative-intent transplant and have lower risk of transplant-related mortality, hence for patients with therapy-related AML, the use of CPX-351 is desirable [8, 9]. For these reasons, patients with therapy-related AML will need an additional score of 2

(not including a score for a history of prior malignancies) in the Hematopoietic Cell Transplantation Comorbidity Index to be considered vulnerable.

Polypharmacy: The list and the number of medications was obtained to determine polypharmacy.

Nutritional status: Mini-nutrition assessment short form is a 6 item screening tool used to evaluate the risk of malnutrition in frail older adults.[35, 36]

Functional status: Function will be assessed using Katz Index of activities of daily living (ADL)[37] and Lawton instrumental activities of daily living (IADL).[38] ADLs are functions of bathing, dressing, toileting, transferring, continence and feeding. IADLs are patient's ability to perform complex tasks such as ability to use telephone, shopping, cooking, housekeeping, laundry, driving, medication management, and management of finances. Mobility, balance, and lower extremity strength will be assessed with the Short Physical Performance Battery.[39]

Social support: The Medical Outcomes Study Social Function Scale is a survey containing 19 items on emotional/informational, tangible, and affectionate support and positive social interaction.[40]

Psychological status: The Patient Health Questionnaire-9 will be used to assess depression. It includes nine items that cover the diagnostic criteria for major depressive disorder.[41] Although depression is associated with mortality [42], the presence of depression is captured by the Hematopoietic Cell Transplantation Comorbidity Index.

Cognition: Montreal Cognitive Assessment will be used to screen for cognitive impairment. It assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.[43]

Physical fitness will be defined based on the abnormalities noted in geriatric assessment into fit or vulnerable. Please see Table 2 for further details. Table 2 will also be used to identify impairments across various domains of geriatric assessment.

Table 2. Definition of Fit and Vulnerable status according to the geriatric assessment

Geriatric Domains	Fit: presence of all criteria	Vulnerable: presence of one or more criteria	Rationale
Hematopoietic Cell Transplantation Comorbidity Index	0-2*	≥3*	A higher score predicts worse survival in AML.[34, 44, 45]
Katz ADL Index (0-6)	6	5 or less	Impairment in ADLs correlates with poor survival in AML and other cancers.[46-48]
Lawton IADL Index (0-8)	8	7 or less	Impairment in IADLs correlates with poor survival in hematologic malignancies.[47, 48]
Short Physical Performance Battery	10-12	9 or less	Impairment correlates with poor survival in AML.[21]
Montreal Cognitive Assessment	≥26	≤25	Cognitive impairment correlates with poor survival in AML.[21]

ADL indicates activities of daily living; IADL indicates instrumental activities of daily living.

*Patients with therapy-related AML will need an additional score of 2 (NOT including a score for a history of prior malignancies) in the Hematopoietic Cell Transplantation Comorbidity Index to be considered vulnerable.

2.3.2 Risk-stratified therapy selection: Patients will be risk stratified based on geriatric assessment and cytogenetic risk categories, as defined by the 2017 European LeukemiaNet (ELN) criteria.[3] Therapy will be selected as per the criteria described in the figure 2.

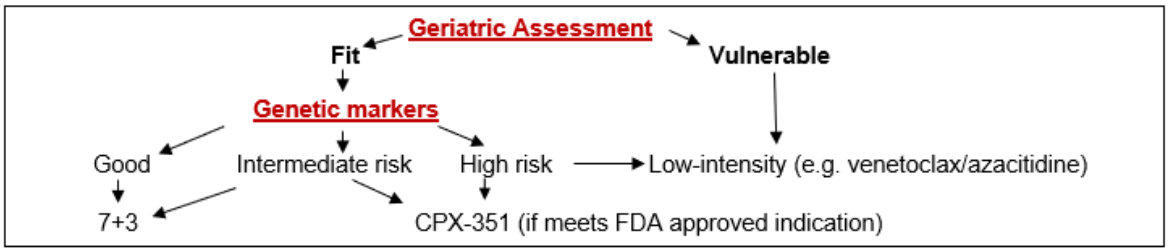

Figure 2. Therapy Selection

Intensive induction used at the discretion of the treating physician may include the combination of infusional cytarabine and idarubicin (7+3) (preferred regimen); CPX-351 (liposomal preparation of cytarabine and daunorubicin, for FDA approved indications) or any other standard of care regimen. Low-intensity induction used at the discretion of the treating physician may include venetoclax in combination with a hypomethylating agent such as decitabine or azacitidine (preferred regimen); venetoclax in combination with low-dose cytarabine; hypomethylating agent; glasdegib in combination with low-dose cytarabine; or any other standard of care regimen.[49] Given its efficacy, venetoclax in combination with a hypomethylating agent would be the preferred low-intensity chemotherapy option.[12, 13]

Intensive chemotherapy such as 7+3 will be used for fit patients (based on geriatric assessment) with good or intermediate risk AML. CPX-351 will be used for fit patients with prior exposure to chemotherapy or radiation, or those with AML with myelodysplasia-related changes, as defined by WHO [10]. Patients, who are deemed vulnerable or those with high-risk AML (not meeting FDA approved indications for CPX-351) will receive low-intensity therapy. These treatment recommendations are consistent with the 2020 National Comprehensive Cancer Network AML guidelines.[49] At the discretion of the treating physician, the addition of targeted agents will be allowed; namely, FLT3 inhibitor (such as midostaurin [11], sorafenib [50] or Gilteritinib[51, 52] in FLT3 mutated patients), or gemtuzumab ozogamicin (in non-FLT3 mutated patients) [7] to either low-intensity such as hypomethylating agent or intensive chemotherapy such as 7+3.

Patients with prior exposure to decitabine or azacitidine may not be treated with decitabine or azacitidine alone but may receive other low-intensity or intensive chemotherapy. Patients with an ejection fraction <45%, or those with significant kidney (e.g. GFR ≤45ml/minute or Creatinine of ≥2 mg/dl) or liver dysfunction (e.g. AST/ALT and/or bilirubin ≥2 times ULN) may receive low-intensity chemotherapy.

2.3.3 Treatment Schedule

Intensive induction and consolidation therapy: Infusional cytarabine and idarubicin is the preferred intensive induction therapy (except in patients meeting the FDA approved indication for CPX-351) (Tables 3 and 4). Intermediate-dose cytarabine is the standard of care consolidation therapy for patients receiving intensive induction therapy (except those treated with CPX-351).[49]

Table 3. Intensive chemotherapy regimen (7+3)

Drug	Dose	Frequency	Number of cycles	Administration
Intensive Induction therapy				
Cytarabine	100-200 mg/m^2	Day 1-7	1	IV infusion
Idarubicin	12 mg/m^2	Day 1-3	1	IV
Intensive Consolidation therapy				
Cytarabine	1000-1500 mg/m^2	Twice daily on Days 1, 3, and 5	2-4, cycles are repeated every 4 weeks	IV

Intensive induction therapy with cytarabine and idarubicin is given for one cycle. Patients who do not respond will receive salvage therapy at the discretion of the treating physician. Once remission is achieved, consolidation therapy will be started. The duration of each cycle of consolidation therapy will be approximately 4 weeks but may

be prolonged by another 2 weeks based on recovery from any toxicities or count recovery in patients with no evidence of disease. Patients who are able to proceed to an allogeneic transplant, or who are not able to tolerate may stop consolidation therapy at the discretion of the treating physician.

Table 4. Intensive chemotherapy regimen (CPX 351)

Drug	Dose	Frequency	Number of cycles	Administration
Intensive Induction therapy for patients meeting FDA approved indication for CPX-351				
CPX 351	Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2	Days 1, 3, 5	1	IV over 90 minutes
Intensive Consolidation therapy for patients treated with CPX 351				
CPX 351	Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2	Days 1, 3	2 cycles, repeated every 5-8 weeks	IV over 90 minutes

Low-intensity induction and consolidation therapy: Venetoclax in combination with hypomethylating agent such as azacitidine or decitabine will be the preferred option (Table 5).

Table 5. Low-intensity chemotherapy regimen

Drug	Dose	Frequency	Number of cycles	Administration
Azacitidine*	75 mg/m^2	Day 1-7	≥3 cycles, repeat every 4-5 weeks	IV
Decitabine*	20 mg/m^2	Daily for 5-10 days	≥3 cycles, repeat every 4-5 weeks	IV
Venetoclax	Variable†	Daily continuously for ≥3 months		PO

*The treating physician may select either azacitidine or decitabine.

†The dose of venetoclax varies depending on drug interaction with antifungal agents. Patients who are not on CYP3A inhibitor, dosing includes 100 mg once on day 1, 200 mg once on day 2, and 400 mg on days 3 and beyond. Patients on posaconazole or other CYP3A inhibitor require dose reduction. For example, a maximum of 70 mg is recommended while on posaconazole, up to 100 mg is recommened while on other strong CYP3A inhibitor, and at least 50% dose reduction is recommended while on moderate CYP3A inhibitor.

The duration of each cycle of hypomethylating agent will be approximately 4-5 weeks but may be prolonged by another 2 weeks based on recovery from any toxicities or count recovery in patients with no evidence of disease. Venetoclax doses may also be interrupted for 2 weeks based on recovery from any toxicities or count recovery in patients with no evidence of disease. Therapy with venetoclax and hypomethylating agent will be continued for 3 or more cycles. Patients who are able to proceed to an allogeneic transplant, or who are not able to tolerate, may stop therapy at the discretion of the treating physician. Therapy continuation beyond 3 cycles will be left up to the discretion of the treating physician.

2.3.4 Dose modifications: All the therapies utilized in this study are considered standard of care.

Intensive therapy: Dose reduction of cytarabine and idarubicin or CPX-351 by up to 50% will be allowed for grade 3/4 toxicities, renal or hepatic toxicities at the discretion of the treating physician.

Low intensity therapy: Dose reduction of venetoclax or hypomethylating agent by up to 50% will be allowed for grade 3/4 toxicities at the discretion of the treating physician.

2.3.5 Supportive care: Supportive care will follow the institutional practice of prophylactic antimicrobials, antiemetics, blood product transfusions, and other supportive care.

2.4 Duration of Study

We estimate that 75 patients will enrolled to this protocol over a 4 year period. The patient will be seen prior to each chemotherapy cycle and as clinically indicated. After the completion of chemotherapy, survival data will be recorded for up to 2 years.

2.5 Assessment Schedule

Complete blood count and chemistry panel will be performed at each of the follow up visits as per the standard of care. Restaging bone marrow aspirate and biopsy will be performed as per the standard of care. For patients receiving intensive chemotherapy, restaging bone marrow biopsy is performed after the intensive induction chemotherapy when blood counts start to recover or after 4-6 weeks of therapy in patients who do not improve blood counts. For patients receiving low-intensity chemotherapy, restaging bone marrow biopsy is performed after the first 1-3 cycles of low-intensity chemotherapy. Routine tests performed on bone marrow aspirate and biopsy include histopathological examination, flow cytometry, genetic and/or molecular tests.

2.6 Post-trial Assessments

Patients who stop the study drug at any time during the trial for any reason will be followed for 30 days after the last day of treatment or until other disease-related treatment begins. For all patients, drug-related adverse events will be followed until baseline, ≤ grade 1 levels, death, or until no further improvement is reasonably expected. Survival data and data regarding disease status will be collected for up to 2 years. Patients may refuse to participate in the post-trial assessments.

2.7 Measurement of Effect

2.7.1 Response criteria: Response criteria and disease progression will be based on definitions provided by the International Working Group.[53] However, prior studies have demonstrated that multiple cycles of low-intensity therapy such as hypomethylating agent may be required to achieve complete remission. [23, 54-58] Hence, patients treated with low-intensity therapy may undergo restaging after more than one cycle. The number of cycles of hypomethylating agent used prior to restaging will be left to the discretion of the treating physician.

2.7.2 90-day mortality: Mortality from any causes within the first 90 days from the time of diagnosis will count towards 90-day mortality.

2.7.3 Geriatric Assessment: At the time of enrollment, and at about 30 +/-14 days and 90 +/-21 days, patients will complete geriatric assessment, as discussed previously.

2.7.4 Symptom burden/Quality of life assessment: At the time of enrollment, 10 +/- 3 days, 30 +/- 7 days and 90 days +/-10 days, patients will complete European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30). EORTC QLQ-C30 is extensively used in cancer studies,[59] and will be utilized to

assess quality of life.

2.7.5 Assessment of neurocognitive status: At the time of enrollment, 10 +/- 3 days, 30 +/- 7 days and 90 days +/-10 days, patients will complete Montreal Cognitive Assessment (MOCA) to assess neurocognitive status. MOCA is easy to use in clinical practice and has high sensitivity and specificity.[43]

2.8 Study Parameters: The study parameters are described below (Table 6).

Table 6. Study parameters

Tests and procedures	**At the time of enrollment (day -7 to enrollment)**	**4 weeks after initiation of chemotherapy or before second cycle of chemotherapy**	**8 weeks after initiation of chemotherapy or before third cycle of chemotherapy**	**90 days after initiation of chemotherapy or before fourth cycle of chemotherapy**
History and Physical Exam	X			
Weight, BMI and KPS	X			
Neurocognitive assessment (MOCA test)[g]	X	X (day 10+/- 3 and 30+/- 7 days)		X (day 90 +/- 10 days)
Quality of life assessment (EORTC QLQ-C30 version 3.0)	X	X (day 10 +/- 3 and 30 +/- 7 days)		X (day 90+/- 10 days)
Disease diagnosis or restaging				
Bone marrow aspirate and biopsy[d]	X	X (consider if count recovery, and no evidence of circulating disease)	X (consider if complete remission is not documented previously)	X (consider if complete remission is not documented previously)
Assessment of comorbidities				
Geriatric assessment	X[a]	X (30 +/- 14 days) (if feasible)[b]		X (90 +/- 21 days) (if feasible)[b]
Echo, MUGA scan or stress echo	X[e]			
Laboratory studies				
CBC	X	X	X	X
CMP	X	X	X	X

Length of stay	For initial diagnosis and chemotherapy only	
Adverse event monitoring[f]		Ongoing from initiation of study drug till 30 days after last administration of study medication[c]

BMI body mass index; CBC complete blood count; CMP Comprehensive metabolic panel; KPS Karnofsky performance status; MUGA scan multigated acquisition scan

a. Includes assessment indicated in table 1. Medical Outcomes Study Social Function Scale can be completed within 48 hours after initiation of chemotherapy.

b. Repeat geriatric assessment will include Mini Nutritional Assessment-Short Form, Weight, body mass index, Katz ADL Index, Lawton IADL Index, Short Physical Performance Battery, Patient Health Questionnaire-9 and Montreal Cognitive Assessment.

c. All grade ≥3 hematological and non-hematological adverse events will be monitored.

d. Routine tests performed on bone marrow aspirate and biopsy include histopathological examination, flow cytometry, cytogenetic, fluorescence in situ hybridization and/or molecular tests. The specific tests performed will be left to the discretion of the treating physician. In a patient with confirmed diagnosis of AML at any time in the past, a repeat bone marrow biopsy is not required at enrollment.

e. As clinically indicated such as in patients planned to undergo intensive chemotherapy. In a patient with an echo or MUGA in the recent past (e.g. 6 months), a repeat test is not required at enrollment.

f. Include data on rehospitalization during the study period

g. Note that version 7.1 original MOCA should be used at time of enrollment visit and day 90 visit; complete version 7.2 Alternative at day 10 and version 7.3 Alternative at the 4 week (30 day) visit.

Survival, disease status and transplant data will be recorded every 3 months for up to 2 years in alive patients.

2.9 Statistical Considerations

2.9.1 Study Design: This is a phase II trial that will evaluate the impact of clinicogenetic risk-stratified management on outcomes of AML in older patients.

2.9.2 Study Population: All patients who receive study drug will be considered evaluable for the safety analysis regardless of the duration of treatment.

2.9.3 Sample size: The study will include a target total of 75 cases of newly diagnosed AML (approximately 15-20 cases per year for 4-5 years).

2.9.4 Sample size justification: An optimal Simon two-stage design [60] was used to test the null hypothesis that 60% versus the alternative of 75% will be alive at 3 months. A sample size of 67 patients will have a minimum power to detect a difference of 80%, and a significance level of 0.05. Accounting for an attrition rate of 10%, a total of 75 patients will be enrolled. PASS 11[61] software was used to conduct all sample size analyses.

2.9.5 Data analysis plan: Data will be descriptively summarized using frequencies and percentages. A *p*-value less than 0.05 will be considered statistically significant unless otherwise specified. All analyses will be performed based on intent-to-treat principle. The method of inversion[62] will be used to generate an interval estimate for the proportion of 90-day mortality. The association between functional status (fit, or vulnerable based on geriatric assessment), and complete remission or 90-day mortality will be explored using a chi-square test [62]. The association between functional status and quality of life and grade 3/4 toxicities will be explored using analysis of variance; if assumptions of analysis of variance fail, Kruskal Wallis will be used. The association between functional status (fit or vulnerable) and neurocognitive status (< 25 or 26 or higher) will be explored using a chi-square test (67). A generalized linear mixed model will be utilized to evaluate changes in quality of life over time. The proportion (and associated 95% confidence interval) of patients with impairments across various domains of geriatric assessment will be presented.

2.9.6 Safety endpoint: All adverse events recorded during the study will be summarized by each subject. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by severity and type of adverse event.

2.9.7 Efficacy endpoints

Complete remission: Complete remission, achieved within 90 +/-10 days of initiation of chemotherapy, will account towards complete remission at 90 days.

Mortality: Mortality at 90 days will be calculated as the time from date of diagnosis to date of death due to any cause by 90 days from diagnosis.

Quality of life: Composite scores, as determined by EORTC QLQ-C30 version 3.0, will be utilized to determine quality of life status. A generalized linear mixed model will be utilized to evaluate changes in quality of life over time.

Neurocognitive status: Composite scores, as determined by MOCA test, will be utilized to determine neurocognitive status.

Overall survival: Overall survival is defined as the time from date of diagnosis to date of death due to any cause. If a subject is not known to have died, survival will be censored at the date of last contact. The Kaplan-Meier method will be used to estimate the survival distributions for each group (fit versus vulnerable). The log-rank test will be used to compare distributions between groups.

2.9.8 Stopping rule: The proposed two-stage design [60] has an expected sample size of 39.35 and a probability of early termination of 0.691 under the conditions specified in the sample size justification. After testing the intervention on 27 evaluable patients in the first stage, the trial will be halted pending data and safety monitoring committee review if 10 or more patients die within 3 months of diagnosis of AML. Patients, who are already enrolled in the study, and are tolerating the study drug may continue the drug. If the trial goes on to the second stage, a total of 67 evaluable patients will be studied. If more than 21 patients die by 3 months of diagnosis of AML, the intervention will be rejected.

CHAPTER 3: RESULTS

We enrolled a total of 36 patients (including 1 patient considered screen failure) between July 2017-December 2019. The pre-planned interim analysis results are based on the first 27 AML patients.

3.1 Demographic characteristics

Of the 28 initial patients, 27 are evaluable. Twelve (44.4%) of the patients are male; 15 (55.6 %) of patients are female. The median age of all patients is 70.1 years with a range from 60.3 to 84.7 years. The median age for males is 67.2 years with a range of 61.1 to 80.3 years; females had a median age of 73.9 years with a range of 60.3 to 84.7 years. Twenty-six (96.3%) reported their race as White and one reported their race as Asian. Twenty-five (88.89%) listed their ethnicity as not Hispanic or Latino; one reported their ethnicity as Hispanic or Latino; one declined to report their ethnicity.

3.2 Results of geriatric assessment

The results of geriatric assessments are shown in the Tables 7 and 8. Median KPS of the enrolled patients was 80% (range 60-100%). About half of the patients had ≥3 comorbidities, impairment in objective physical function (short physical performance battery) and Montreal Cognitive Assessment (Table 8). Additionally, 67% had poor nutritional status (MNA score of ≤11) and 26% had abnormal depression screen (PHQ-9 score of ≥10). Please see section 2.3.1 for normal values.

Table 7. Results of geriatric assessment

Assessment Score	Mean	Std Dev	Median	Min	Max
Hematopoietic Cell Transplantation Comorbidity Index	2.5	2.1	2	0	7
Mini-Nutritional Assessment-SF	10.1	2.3	10	6	14
Katz ADL	5.4	1.1	6	1	6
Lawton ADL	7.5	1.3	8	2	8
Short Physical Performance Battery	7.0	4.1	9	0	12
Patient Health Questionnaire 9	6.7	4.8	6	0	17
KPS Score	78.2	11.0	80	60	100
MOCA	24.2	3.8	24	13	29

Table 8. Definition of Fit and Vulnerable status according to the geriatric assessment

Geriatric Domains	Fit: all criteria (scores)	Vulnerable: one or more criteria (scores)	% meeting threshold for vulnerable
Comorbidity Burden			
Hematopoietic Cell Transplantation Comorbidity Index (HCTCI)	0-2[a]	3 or more	13 (48%)
Physical Function			
Katz activities of daily living (ADL) index	6	5 or less	11 (41%)
Lawton instrumental ADL (IADL) index	8	7 or less	5 (19%)
Short Physical Performance Battery (SPPB)	10 – 12	9 or less	16 (59%)
Cognitive function			
Montreal Cognitive Assessment	26 - 30	25 or less	16 (59%)

The number indicates scores of different tests.

[a]Patients with therapy-related AML would need ≥ 2 score in addition to the history of prior malignancy to be considered vulnerable. This modification was allowed to not limit the use of CPX 351.

The median number of geriatric domains meeting vulnerable criteria per patient was 2 (range 0 to 4). Three patients were deemed fit, 4 patients met only one vulnerable criteria (high HCT CI), and others met 2-4 vulnerable criteria (Table 9).

Table 9. Number of subjects meeting vulnerable criteria. X denotes assessment domain scored as vulnerable.

Number of criteria met	Count (%)	Pattern Count	HCTCI	Katz ADL	Lawton ADL	SPPB	MOCA
0	3 (11)	3					
1	4 (15)	4	X				
2	6 (22)	3				X	X
		2		X		X	
		1	X				X
3	11 (41)	2		X		X	
		1		X			
		1		X			
		3	X				
		2	X				
		1	X	X			
4	3 (11)	2		X	X	X	X
		1	X	X		X	X

3.2.1 Comorbidities: A total of 45 comorbidities under the HCT CI were observed across the 27 evaluable subjects; the median number of comorbidities was 2 with a range of 0-5 (Table 10). Cardiovascular comorbidities, depression/anxiety, diabetes, and prior solid malignancy represented the most common comorbidities in the study population (Table 11).

Table 10. Number of comorbidities per patient

Number of comorbidities	Count (%)	Comments
0	6 (22.2)	2 subjects fit/4 subjects vulnerable
1	7 (25.9)	1 subject fit/6 subjects vulnerable
2	8 (29.7)	All subjects vulnerable
3	4 (14.8)	All subjects vulnerable
4	0 (0.0)	
5	2 (7.4)	All subjects vulnerable

Table 11. Types of comorbidities

Comorbidity under HCT CI	Number of subjects with comorbidity
Arrhythmia	3
Cardiovascular	8
Cerebrovascular	1
Depression / anxiety	7
Diabetes	6
Heart valve disease	0
Hepatic mild	0
Hepatic moderate / severe	1
Infection	1
Inflammatory bowel disease	2
Obesity	3
Peptic ulcer	1
Prior solid malignancy	7
Pulmonary Moderate	2
Pulmonary Severe	1
Renal	1
Rheumatologic	1

3.3 AML characteristics

One patient each had myeloid sarcoma and therapy-related myeloid neoplasm; all other patients had AML. Median WBC of enrolled patients at diagnosis was 8400/mm^3 (1200-10400/mm^3), and median bone marrow blast percentage was 36% (12-91%). Other laboratory data at diagnosis are shown in the table 12.

Table 12. Laboratory data

Lab	Median	Min	Max
WBC/mm^3	8400	1200	104000
Hemoglobin, g/dl	8.5	5.7	13.1
Platelet Count/mm^3	94000	13000	366000
Absolute Neutrophil/mm^3	1600	0	38700
Bone Marrow Blast Percentage	36	12	91

3.3.1 AML risk categories and mutations: ELN risk categories included adverse (63.0%), intermediate (18.5%), and good-risk AML (18.5%). The count (percentage) of mutations present at enrollment are summarized in Table 13. The most common mutations included TET2 and ASXL1 (22.2%), TP53 and NPM1 (18.5% each), IDH1 and RUNX1 (14.8% each).

Table 13. Mutational analysis results

Mutation	Presence					
	Yes, N(%)		Unknown, N(%)		No, N(%)	
FLT3ITD	2	(7.4)	3	(11.1)	22	(81.5)
FLT3TKD	0	(0.0)	7	(25.9)	20	(74.1)
NPM1	5	(18.5)	2	(7.4)	20	(74.1)
Biallelic CEBPA	1	(3.7)	7	(25.9)	19	(70.4)
IDH1	4	(14.8)	3	(11.1)	20	(74.1)
IDH2	2	(7.4)	3	(11.1)	22	(81.5)
RUNX1	4	(14.8)	6	(22.2)	17	(63.0)
ASXL1	6	(22.2)	8	(29.7)	13	(48.1)
TP53	5	(18.5)	6	(22.2)	16	(59.3)
DNMT3A	2	(7.4)	7	(25.9)	18	(66.7)
EZH2	1	(3.7)	7	(25.9)	19	(70.4)
TET2	6	(22.2)	8	(29.7)	13	(48.1)

3.4 Chemotherapy use

Three patients received intensive chemotherapy; CPX 351 (n=2) or 7+3+ gemtuzumab (n=1). Other patients received decitabine or azacitidine alone (n=16), azacitidine and venetoclax (n=5) or decitabine and midostaurin (n=3). The median time from diagnosis to therapy initiation was 7 days (0-20 days) whereas the median time from enrollment to therapy initiation was 2 days (range 0-9).

3.5 Mortality results

Mortality at 30 days from diagnosis was 3.7% (95% confidence interval, CI 0.7-18.3%) and at 90 days was 29.6% (95% CI 15.9-48.5%) (Figure 3). Historical control was derived from older adults aged ≥60 years treated with either intensive or low-intensity chemotherapy between the years 2011-2016.[63]

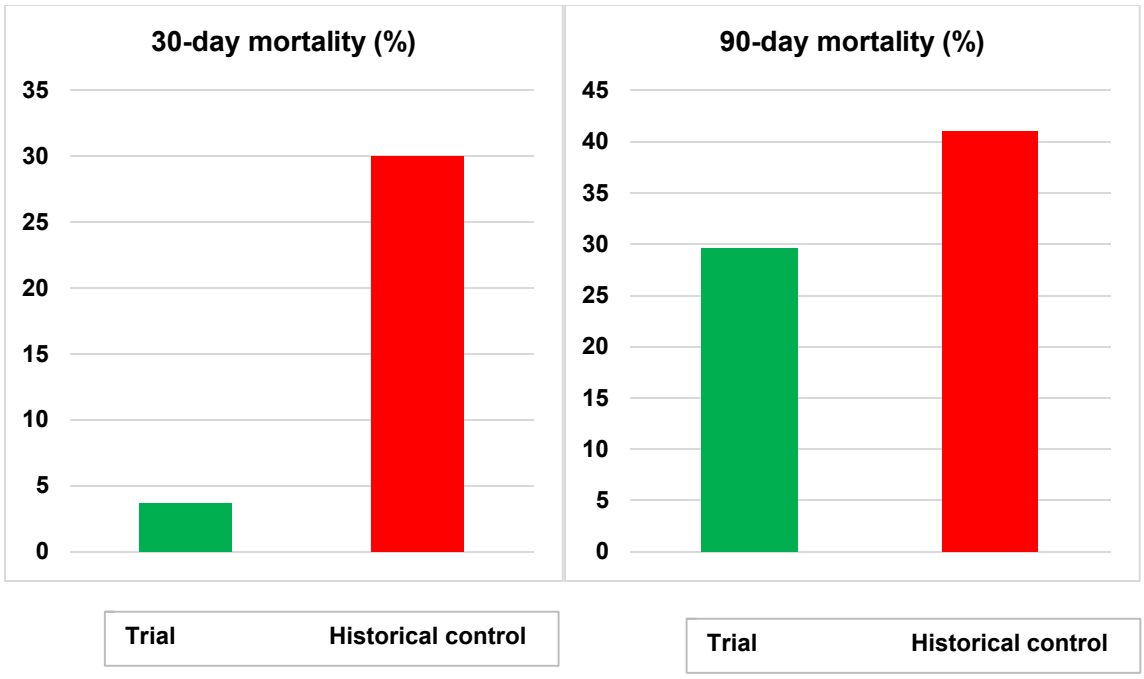

Figure 3. 30-day and 90-day mortality results

CHAPTER 4: DISCUSSIONS

The management of AML is complex in older patients because of associated comorbidities, intolerance to high-dose chemotherapy, and high-risk tumor biology. The outcomes of older patients, who are unfit, or have high-risk AML are poor with chemotherapy.[32] In these patients, induction mortality is high (10-40% depending on age and performance status[22]), and long-term survival at 5 years is less than 10-20%.[16, 17] In older patients with AML, previous studies have demonstrated that geriatric assessment uncovers significant functional impairments [18] and predicts toxicities and overall survival.[19-21] Studies in AML have clearly demonstrated the influence of leukemia cytogenetics on the probability of survival with intensive chemotherapy.[30, 31] Given the powerful impact of leukemia cytogenetics and functional status determined by geriatric assessment on outcomes, we integrated these multidimensional assessments into clinicogenetic risk-stratification strategy. While the cytogenetic risk category can provide a probability to achieve complete remission with chemotherapy, the findings of geriatric assessment can predict anticipated toxicity risk. Thus, a combination of clinical parameters such as level of fitness of patients as measured by geriatric assessment, and cytogenetic features of leukemia can provide a strategy to individualize therapy selection.

In our study population, 48% had a HCT CI of 3 or more. Cardiovascular comorbidities, depression/anxiety, diabetes, and prior solid malignancy represented the most common comorbidities. Our study also demonstrated a high frequency of impairment in objective physical and cognitive function detectable by geriatric assessment. This is consistent with results of prior studies that have utilized geriatric

assessment in older adults with AML.[18] The median number of geriatric domains meeting vulnerable criteria per patient was 2 (range 0 to 4). Three patients were deemed fit, 4 patients met only one vulnerable criteria (high HCT CI), and others met 2-4 vulnerable criteria.

The percentage of good-risk AML in our population was higher than expected, possibly an incidental finding because of a small sample size. The most common mutations included ASXL1 and TET2 (22.2%), TP53 and NPM1 (18.5% each), IDH1 and RUNX1 (14.8% each). A myeloid mutation panel was performed as clinically indicated, hence not all patients underwent myeloid mutation panel. Also, our study included both de novo AML as well as patients with prior cancer. With these caveats, the mutation results are largely consistent with published literature.

Patients were able to start therapy within a median of 2 days following enrollment, thus demonstrating the feasibility of our personalized approach to use geriatric assessment and genetic profiling results to select treatment. We noted a high rate of use of low intensity chemotherapy that is likely explained by broad eligibility criteria, stringent criteria to define fitness, and physicians' preference to enroll vulnerable patients to this trial.

Our pre-planned interim analysis data appear promising with lower rates of early mortality compared to unmatched historical control of patients ≥60 years, who were treated at our center between 2011-2016. The 30-day mortality for historical control was 30% (95% CI 22-40%) and 90-day mortality was 41% (95% CI 32-52%).[63] The mortality results were also comparable to results of other prior studies, as demonstrated in the table 14.

Table 14. Early mortality in prior trials in older adults with AML

Population	30-day mortality	60 or 90-day mortality
Current trial	3.7%	29.6% at 90 days
Decitabine vs LDAC[64]	8-9%	19.7%-23% at 60 days
Aza vs CCR[55]	6.6-10%	16.2-18.2% at 60 days
7+3[17]	11-12%	
CPX 351 vs 7+3[65]	5.9-10.6%	13.7-21.2% at 60 days
Ven-LDAC[66]	6%	
Ven-HMA[67]	3%	8% at 60 days
E2906 trial[68]	7.9-8.5%	13.1-14.9% at 60 days

7+3 7-day cytarabine and 3-day anthracycline, Aza azacytidine, CCR conventional care regimen, CPX 351 liposomal daunorubicin and cytarabine, HMA hypomethylating agent, LDAC low-dose cytarabine, Ven venetoclax

Our trial has certain limitations. This was a small single-center trial that largely enrolled white population. Our trial was not a randomized trial and utilized a historical control which has limitations in terms of potential differences in patients' characteristics. Also, there has been approval of novel drugs in more recent years. These factors may potentially limit generalizability of our results.

Despite these limitations, our trial was an important study with several strengths. First, it attempted to answer questions that have remained elusive. The trial provided an objective model to define fitness for intensive chemotherapy in a prospective trial. Secondly, this is a unique oncology trial that has utilized both disease factor (genetic profiling) and patient profiling (geriatric assessment) to advance personalized medicine, unlike the vast majority of other precision medicine trials that tend to focus only on genomic factors. Our trial also had important pragmatic aspects such as broad eligibility criteria, flexibility of chemotherapy choices, and co-management of patients with community oncologists. The 2010 Institute of Medicine report indicates that about 3% of all cancer patients enroll in clinical trials in the United States.[69] Studies with broad

eligibility criteria can improve enrollment in general as well as enrollment of patients who are generally excluded in other trials. Such patients include patients with organ dysfunction, other co-existing comorbidities, or another cancer. Patients with AML who are managed in community centers often do not participate in clinical trials. A trial such as ours is a step towards capturing such patients.

In conclusion, our model to personalize AML therapy selection represents an innovative approach to precision medicine that incorporates both geriatric assessment for patient profiling and genetic profiling of leukemia cells. Who can tolerate and benefit from intensive chemotherapy is an important unanswered question in the field of older adults with AML. Our study is a step towards answering this question. The results of our interim analysis demonstrates feasibility of personalized therapy. We were able to initiate therapy within 2 days of enrollment, and our early mortality results appear promising. The phase II trial is ongoing and will assess the outcomes of the fully powered cohort and also will analyze longer-term survival. Future research should consider a randomized control trial to confirm the value of personalized therapy selection in reducing early mortality in older adults with AML.

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