Title: A phase II study of the impact of clinicogenetic risk-stratified management on outcomes of acute myeloid leukemia in older patients

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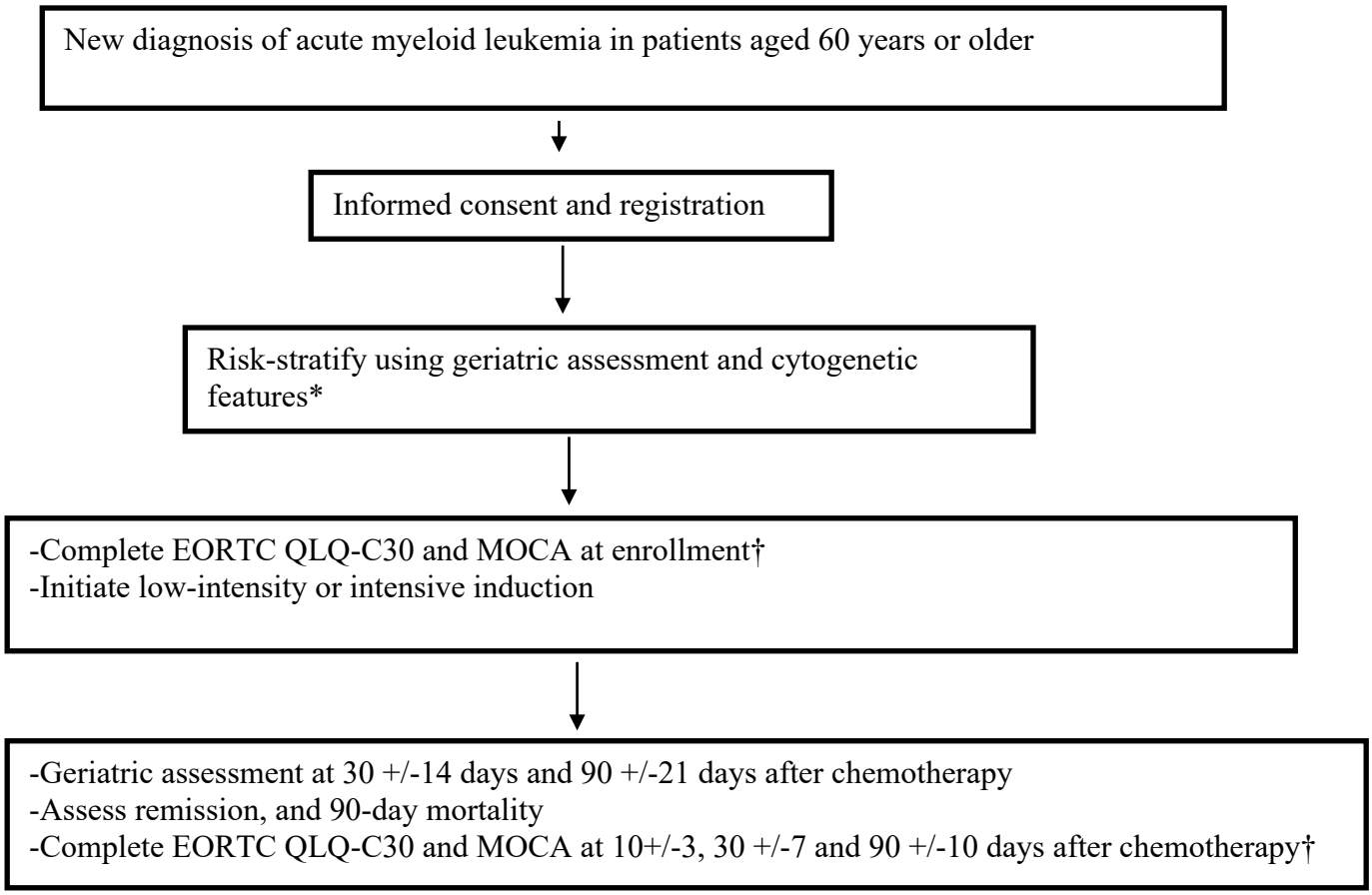
Study Schema



*Patients will be risk stratified based on geriatric assessment and cytogenetic risk categories, as defined by the 2017 European LeukemiaNet (ELN) criteria (1). Intensive induction used at the discretion of treating physician may include combination of infusional cytarabine and idarubicin (7+3) (preferred regimen); CPX-351 (liposomal preparation of cytarabine and daunorubicin, preferred agent for FDA approved indications) or any other standard of care regimen. Low-intensity induction used at the discretion of treating physician may include hypomethylating agent such as azacitidine or decitabine and venetoclax (preferred regimen); hypomethylating agent, or any other standard of care regimen. Enrollment in other clinical trials are permitted. Intensive chemotherapy such as 7+3 will be used for fit patients (based on geriatric assessment) with good or intermediate risk cytogenetics. CPX-351 will be used for fit patients with prior exposure to chemotherapy or radiation, or those with AML with myelodsyplasia-related changes, as defined by WHO (2). Patients, who are deemed vulnerable or those with high-risk AML (not meeting FDA approved indications for CPX-351) will receive low-intensity therapy. The addition of targeted agents namely, FLT3 inhibitor (such as midostaurin (3) or sorafenib (4) in FLT3 mutated patients), or gemtuzumab ozogamicin (in non-FLT3 mutated patients) (5) to either low-intensity such as hypomethylating agent or intensive chemotherapy such as 7+3 will be allowed.

† EORTC QLQ-C30 indicates European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30, and MOCA indicates Montreal Cognitive Assessment.

Abstract:
Title: A phase II study of the impact of clinicogenetic risk-stratified management on outcomes of acute myeloid leukemia in older patients
Objectives: To determine the rate of complete remission, and mortality at 90 days in the entire cohort of older patients (≥60 years) with newly diagnosed acute myeloid leukemia, who receive clinicogenetic risk-stratified therapy allocation
Eligibility: Older patients (≥60 years) with acute myeloid leukemia
Intervention: Subjects will receive standard of care intensive or low-intensity induction based on cytogenetic and geriatric assessment-based risk stratification, as demonstrated in the study schema.
Evaluation: Subjects will be evaluated for disease status, survival, quality of life and neurocognitive status for 90 days and then followed for a total of 2 years for survival data.

Section 1.0 Objectives:

Primary objectives:

1. To determine the rate of complete remission and 90-day mortality in the entire cohort of older patients (≥60 years) with newly diagnosed acute myeloid leukemia (AML), who receive clinicogenetic risk-stratified therapy allocation

Secondary objectives:

1. To determine the rate of complete remission and 90-day mortality in subsets of older patients who receive intensive and low-intensity chemotherapy
2. To assess the impact of baseline functional status (measured by geriatric assessment) on mortality in older patients, who receive clinicogenetic risk-stratified therapy allocation
3. To determine the symptom burden/quality of life, and functional status at diagnosis and following initiation of chemotherapy
4. To determine proportion of patients with impairments detected by geriatric assessment
5. To calculate the percentage of older patients who receive allogeneic stem cell transplant during the study period
6. To assess overall survival at 1-year for the entire cohort of older patients

Correlative Objectives

1. Determine whether expression levels of inflammatory cytokines are regulated by miRNAs in patients with AML.

Section 2.0 Introduction:

Acute myeloid leukemia (AML) is among the most common hematologic malignancies in adults and is commonly diagnosed in sixth or seventh decades of life (6). AML accounts for approximately 10,000 deaths in the United States every year (7). 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 (1) (Appendix A).

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 one-third 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 real world (8-10). Longer-term survival has not improved significantly in 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. In 2017, 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 risk AML (5). CPX-351(11, 12) is FDA-approved(13) (because of survival benefit over 7+3) for patients with prior exposure to chemotherapy or radiation, or those with certain genetic markers (AML with myelodsyplasia-related changes, as defined by WHO (Appendix B) (2)). The addition of FLT3 inhibitor midostaurin (3) in FLT3 mutated patients is also associated with survival benefit. In 2018, the FDA approved venetoclax (accelerated approval) (inhibits the anti-apoptotic protein BCL-2) and glasdegib (small molecule inhibitor of the Hedgehog pathway) for AML. Venetoclax received full FDA approval in 2020 in combination with low-dose cytarabine (LDAC) or hypomethylating agents, decitabine or azacitidine.(14-16) Glasdegib is approved in combination with LDAC.(17)

2.1 Value of individualized therapy selection

In older patients with AML, practical and rational therapy selection is crucial to receive chemotherapy 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.(18, 19) Such patients are likely to benefit from intensive chemotherapy. Conversely, many older patients have significant comorbidities requiring multiple medications, cognitive impairment, or malnutrition, and are not physically fit to reap the benefit of intensive chemotherapy.(20-23) 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.(24) Such patients may be better served with low intensity chemotherapy rather than intensive chemotherapy. Hence, individualized therapy selection should balance both anticipated benefits and risks of toxicities.

2.2 Current risk-stratification and 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.(25, 26) Additionally, for many older patients, except for those with good-risk cytogenetic, the goal of initial chemotherapy should be to allow eligible patients to undergo allogeneic hematopoietic cell transplant because transplant, compared to chemotherapy alone, becaue transplant offers a significantly higher possibility of long-term disease control in high-risk patients.(27) 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 from the safe use of allogeneic transplant.(28, 29) Until recently, low intensity chemotherapy options resulted in low rates of complete remission and a small probability of undergoing an allogeneic transplant. 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 combination chemotherapy in patients who are not fit to receive intensive chemotherapy.

2.3 Integration of geriatric assessment in risk-stratified management

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,(20) uncovers significant functional impairments(20) and predicts toxicities and overall survival.(21-23) Hence, geriatric assessment is considered superior to therapy allocation based on assessment of age and performance status.(6) 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.(30) Based on these rationale, the NCCN guidelines(31) and Cancer and Aging Research Group(32) recommend integrating geriatric assessment in therapeutic decision-making.

2.4 Impact of leukemia cytogenetics on outcomes of intensive chemotherapy

Studies in AML have clearly demonstrated the influence of leukemia cytogenetics on the probability of complete remission and survival with intensive chemotherapy.(33, 34) Good-risk AML in fit older patients is associated with a high complete remission rate (up to 80%(18, 19)) and survival (60% at 2 years(19) and 40% at 5 years(18)) when treated with intensive chemotherapy such as anthracycline and cytarabine (7+3), 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.(35) In these patients, at best, complete remission rates are 30-60%, induction mortality is high (10-40% depending on age and performance status(24)), and long-term survival is less than 10-20%.(18, 19) Although beneficial, allogeneic transplant is not feasible in many older patients, in part because of induction mortality and functional decline from intensive chemotherapy.(28, 29) Recently, CPX-351(11, 12) has demonstrated survival benefit over 7+3 for patients with prior exposure to chemotherapy or radiation, or those with certain genetic markers (AML with myelodsyplasia-

related changes, as defined by WHO (2). For this reason, CPX-351 received FDA approval in these subsets of patients.

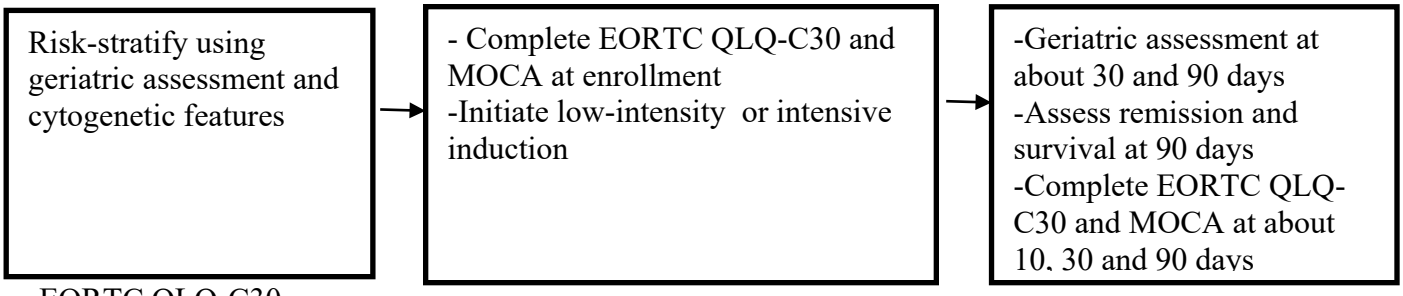
2.5 Use of hypomethylating agent and other novel combination therapies

The use of hypomethylating agents such as decitabine therapy for 5 days, or 7-day course of azacitidine has been extensively studied in older unfit patients with AML.(25, 36, 37) In these studies, hypomethylating agents have improved survival despite a lower probability of complete remission with hypomethylating agents.(25, 36, 37) Importantly, hypomethylating agents such as decitabine therapy results in comparable remission rate within different risk categories of AML, thus indicating that such an approach may be particularly of value in high-risk AML.(36-40) In more recent years, venetoclax is approved in combination with low-dose cytarabine (LDAC) or hypomethylating agents, decitabine or azacitidine; such combination increases the rates of remission as well as survival.(14-16) The use of newer low intensity chemotherapy combinations in unfit older patients or those with high-risk AML, with complete remission rate largely comparable to intensive chemotherapy, may increase tolerability, and reduce the risk of decline in quality of life, and cognitive status. This is particularly important for older patients who frequently value maintenance of quality of life and cognitive status over living with functional or cognitive impairment.(41)

2.6 Study Schema and Rationale

Given the powerful impact of leukemia cytogenetics and functional status determined by geriatric assessment on outcomes, we aim to integrate these multidimensional assessments into clinicogenetic risk-stratification strategy, as highlighted in the schema of this study (Figure 1). 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 chemotherapy while reducing the risk of serious toxicities because of intolerance to chemotherapy.

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.

Cytogenetic analysis can delay initiation of therapy, however, prior studies have indicated that overall survival is not compromised as a result of delay in time to initiation of

therapy in stable older patients with AML.(42, 43) Although hypomethylating agent has been utilized in patients with high blast count,(38, 44) the time to response to hypomethylating agent is generally longer than intensive chemotherapy, hence hypomethylating agent alone may not be appropriate in patients with aggressive disease pace (e.g. those with leukostasis).(38-40) Hence, patients requiring urgent chemotherapy initiation (in addition to debulking agent such as hydroxyurea or cyclophosphamide, or leukapheresis) will be excluded from this study. Assessment of quality of life and neurocognitive status at baseline and at 90 days after initiation of therapy will determine to which extent these parameters are preserved.

2.7 Inflammatory cytokines

Inflammatory cytokines can serve as important biomarkers of frailty, quality of life and survival. Cytokines such as interleukin-6 are implicated in the development of frailty in older adults without any malignancy.(45) In patients with solid malignancies; systemic inflammation contributes to growth and progression of cancer,(46, 47) and inflammatory markers correlate with quality of life,(48, 49) cognition(50) and survival.(51-56) Inflammatory markers affect mortality in patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplant.(21, 57) In a study of AML and myelodysplastic syndrome (MDS), interleukin-6 and 8 correlated with cognition, and IL-6, IL-1RA, and TNF-alpha levels correlated with fatigue.(58) Another study of AML patients demonstrated a correlation between TNF-alpha and fatigue.(59) These hypothesis-generating studies included only a limited panel of cytokines, both younger and older patients, patients with MDS as well (in one study(58)) and did not capture frailty.(58, 59) Other studies in AML and MDS have demonstrated a correlation between certain cytokines and survival.(60-62) In two of the largest study published to date, however, the treatment was heterogeneous and different from the current standard of care.(62, 63) The studies included both younger and older patients,(62, 63) and in one study, patients with MDS and patients with both newly diagnosed and relapsed disease.(62) While these studies lay a strong foundation to highlight the potential candidacy of inflammatory cytokines to be biomarkers of frailty, and quality of life, further studies are needed in a homogenous study population of older adults with AML, who are predominantly treated with chemotherapy used in the contemporary era.

2.8 MicroRNAs

miRNA-cytokine profiling can provide mechanistic insights of regulatory pathways involved in inflammation-mediated frailty in older adults with AML and allow development of miRNA-based biomarkers and therapeutic approaches. miRNAs mediate regulation of tumor microenvironment, and cytokines and may modulate pathways involved in chemotherapy resistance and progression of AML.(64) For example, cytokines such as IL-3, GM-CSF and G-CSF are predominant regulators of growth and differentiation of myeloid progenitors.(65-67) Studies have demonstrated correlation between miRNA signatures and cytogenetic risk-groups, and microRNA-expression signatures as prognostic biomarkers in patients with AML with normal karyotypes. miRNA-based biomarkers offer an advantage of being more stable over time than longer, coding mRNAs used in gene expression profile (GEP) analyses.(68) Current research efforts are focused on validation of functional aspects of miRNA expression in AML**.** Expression of 452 genes significantly correlated with the prognostically relevant miRNA-expression signature. These genes included genes encoding proteins involved in innate immunity, such as intracellular sensors of microbial components and cell injury (part of "inflammasome" regulating activation of caspase-1 and interleukin-1β). Although the direct

involvement of miRNAs in AML has been suggested, their role in the regulation of cytokines expression, inflammation-mediated frailty and patient outcomes need further elucidation. Our analyses to understand the cytokine network in relation to miRNA could allow the development of miRNA-based biomarkers and therapeutic approaches in the future.

Section 3.0 Eligibility Criteria:

Study population will include eligible older patients with histologically confirmed newly diagnosed acute myeloid leukemia.

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.

Inclusion of Women and Minorities
Both men and women and members of all races and ethnic groups are eligible for this trial.

Section 4.0 Registration Procedure:

Subjects, who are referred to the Nebraska Medical Center (NMC)/UNMC or other IRB approved participating sites, with histologically confirmed AML may be eligible for this trial.

Screening eligibility based on standard clinical care will be performed by the treating physician at the time of initial diagnosis of AML. During the time of diagnosis of AML, a history and physical examination is performed, laboratory data obtained, and performance status is assessed. Blood and bone marrow studies obtained may include a complete blood count, bone marrow aspirate and biopsy with morphologic assessment, flow cytometry, karyotyping, fluorescence in situ hybridization (FISH) studies and molecular mutations. Radiologic/imaging evaluations will be performed as clinically indicated and is at the discretion of the treating physician. Any pathologic specimens obtained at referring institutions will be reviewed for accuracy. The subject's treating physician will make the decision as to eligibility of the candidate based on the eligibility criteria listed above, prior to offering consent.

If the subject is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the subject after thorough review of the study is completed with the physician and his/her designee.

NOTE: Problems related to insurance coverage for UNMC potential subjects or enrolled subjects will be reported to the IRB as they are encountered.

Some insurance carrier's may decline to cover the costs of usual medical care if the subject is participating in a clinical trial. The subject will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The subject can then decide if they wish to participate.

4.1 Eligibility Verification/Registration
Before patients are enrolled into the study, an eligibility checklist (Appendix C) must be completed to verify the subject meets the eligibility criteria. Date of enrollment is defined as the date of the start of study treatment/first protocol related intervention. The eligibility check list will be maintained in the study file.

All study patients will be registered through the sponsor site (UNMC) by contacting the UNMC Project Coordinator. All study personnel from UNMC and non-UNMC IRB approved sites will contact the UNMC Research Project Coordinator if a patient appears to meet the eligibility criteria. They will email the completed eligibility checklist (Appendix C) and de-identified

signed consent form document to the Research Project Coordinator to verify the subject meets the eligibility criteria. Once the UNMC Research Project Coordinator confirms that the patient meets criteria, and target accrual has not been met, approval for the patient will be given and study subject number assigned. A confirmation of registration will be forwarded by the UNMC Research Project Coordinator to the site.

In the event of an after-hours potential enrollment (i.e., clinic coast time differences), or an immediate need for convenience for the subject, please contact the sponsor PI.

UNMC study personnel will provide the UNMC Fred & Pamela Buffett Cancer Center PRMS office and the study project coordinator an electronic copy of the signed and dated consent form for each UNMC subject registered to the protocol within 7 days that includes the following information:

- Protocol Number
- Patient Identification: Patient's name, medical record number
- Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity
- Patient zip code/country (if not USA) and
- primary method of payment information

The UNMC Research Project Coordinator will provide the following listed information to the UNMC Fred & Pamela Buffett Cancer Center PRMS office for participating affiliate and non-UNMC IRB approved sites. The listed information will be provided to the PRMS office within one week of enrollment as applicable:

  - UNMC and Participating Site Protocol Numbers
  - Investigator/Participating Site Identifier (ID)
  - Subject ID: Assigned by UNMC [Site ID followed by, initials and subject number (##-FML initials-###)]
  - Consent Date: Date subject signed consent
  - Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity, patient zip code/country
  - Primary method of payment information
  - Re-consent Date: (If applicable)
  - Ineligibility Status: (If known)
  - Off Study Date: (If applicable)

Section 5.0 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.

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

5.1.1. Comorbidity: Comorbidity burden will be calculated according to the Hematopoietic Cell Transplantation Comorbidity Index score (Appendix D).(69) It predicts treatment-related mortality and is more sensitive than the Charlson Comorbidity Index in older adults with AML.(70) Many patients may not have undergone a pulmonary function test or an echocardiogram prior to enrollment. In the absence of a known diagnosis of chronic pulmonary obstructive disease or other pulmonary disease, or congestive heart failure, such patients will receive a score of 0 for pulmonary comorbidity and congestive heart failure. The use of prophylactic antibiotics or fevers thought to be possibly related to tumor fever may not be used to assign a score of 1 for infection. A prior diagnosis of solid or lymphoid malignancies but not myelodysplastic syndrome or other myeloid malignancies gets a score of 3 for prior malignancy. Additional clarification may be obtained from the expert review paper by Sorror (71), who designed the tool.

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 (11, 12). 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.

5.1.2 Polypharmacy: The list and the number of medications will be obtained from history and physical exam.

5.1.3 Nutritional status: Mini-nutrition assessment short form is a 6-item screening tool used to evaluate the risk of malnutrition in frail older adults.(72, 73)

5.1.4 Functional status: Function will be assessed using Katz Index of activities of daily living (ADL)(74) and Lawton instrumental activities of daily living (IADL).(75) 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.(76)

5.1.5. 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.(77)

5.1.6 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.(78) Although depression is associated with mortality (79), the presence of depression is captured by the Hematopoietic Cell Transplantation Comorbidity Index.

5.1.7 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.(80)

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,* Weight loss/body mass index
Functional status ADL IADL Mobility	 Katz ADL Index Lawton IADL Index 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 (Appendix G)

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.

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.(70, 81, 82)
Katz ADL Index (0-6)	6	5 or less	Impairment in ADLs correlates with poor survival in AML and other cancers.(83-85)
Lawton IADL Index (0-8)	8	7 or less	Impairment in IADLs correlates with poor survival in hematologic malignancies.(84, 85)
Short Physical Performance Battery	10-12	9 or less	Impairment correlates with poor survival in AML.(23)
Montreal Cognitive Assessment	≥26	<25	Cognitive impairment correlates with poor survival in AML.(23)

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. Please see section 5.1.1 for further details and rationale.

5.2 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 (1) (Appendix A and B). Therapy will be selected as per the criteria described in the figure 2.

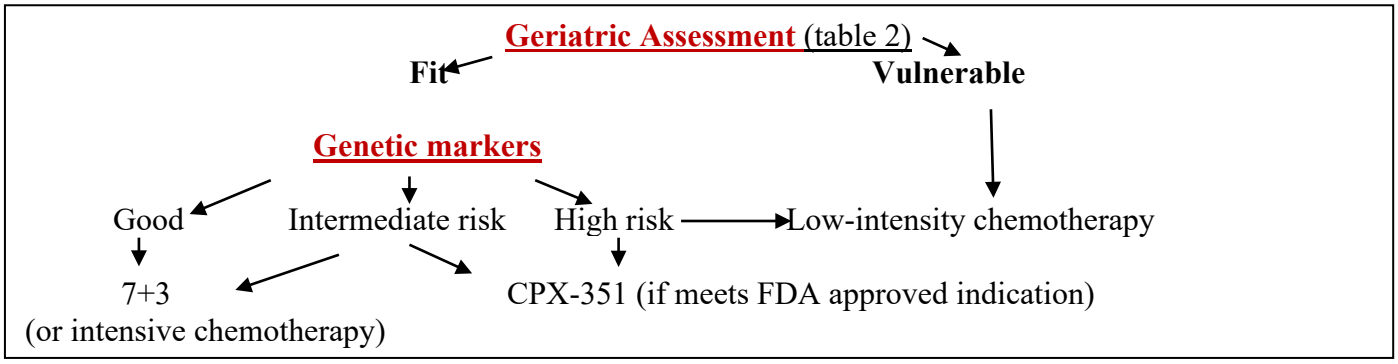


Figure 2. Therapy Selection.

Intensive induction used at the discretion of treating physician may include 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 treating physician may include venetoclax in combination with hypoemthylating 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. Given its efficacy, venetoclax in combination with hypoemthylating agent would be the preferred low-intensity chemotherapy option.(14, 15) Enrollment in other clinical trials are permitted.

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 myelodsyplasia-related changes, as defined by WHO (2). Patients, who are deemed vulnerable or those with high-risk AML (not meeting FDA approved indications for CPX-351) will receive low-intensity therapy. At the discretion of the treating physician, the addition of targeted agents namely, FLT3 inhibitor (such as midostaurin (3), sorafenib (4) or Gilteritinib(86, 87) in FLT3 mutated patients), or gemtuzumab ozogamicin (in non-FLT3 mutated patients) (5) to either low-intensity such as hypomethylating agent or intensive chemotherapy such as 7+3 will be allowed.

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 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.

While the study allocates intensive or low-intensity therapies based on risk-stratification, all the therapies used in this study are considered standard of care for patients with AML. For the purpose of this study, a combination of infusional cytarabine and idarubicin (7+3) is the preferred intensive therapy (except in patients meeting the FDA approved indication for CPX-351), and venetoclax in combination with hypomethylating agent is the preferred low-intensity therapy. When possible, patients who receive intensive induction, are encouraged to receive intensive consolidation as per the standard of care. A general guidelines for the dosing and dose modifications of chemotherapy are presented here, however, final decisions regarding selection of specific therapy, dose modification and the use of supportive care will be left to the discretion of the treating physician.

5.3 Treatment Schedule

5.3.1. 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). Intermediate-dose cytarabine will be used as the standard of care consolidation therapy for patients receiving intensive induction therapy (except those treated with CPX-351).

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 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.

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

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

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. Given the focus of the study on early mortality, therapy continuation beyond 3 cycles will be left up to the discretion of the treating physician.

5.4 Dose modifications
All the therapies utilized in this study are considered standard of care. Thus, treating oncologists are familiar with these drugs and dose modifications.

5.4.1. 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.

5.4.2. 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.

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

5.6 Duration of Study: We estimate that 75 patients will enrolled to this protocol over a 4 year period.

5.6.1 Duration of Follow up: 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.

5.7 Assessment Schedule: CBC 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 count. 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.

5.8 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 SAEs and AEs 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.

5.9 Criteria for Removal from Study:
Patients will discontinue the study drug for any of the following reasons:

- Progression of disease
- If the patient experiences an adverse reaction that, in the opinion of the investigator, necessitates the cessation of the study drug, including any unresolved serious adverse event.
- Any patient who suffers a serious systemic allergic response or severe degree of intolerance to the study medication will be withdrawn from further study treatment
- Development of intercurrent medical problems that would make continued protocol therapy detrimental to the patient's safety.
- The patient chooses to discontinue treatment.

Patients who stop study drug may complete follow-up surveys and assessments at their routine clinic visits, if agreed upon by the patients. Data may continue to be collected via chart review, if agreed upon by the patients.

Patients will be removed from the study (study withdrawal) for any of the following reasons:

- If at any time the constraints of this protocol are detrimental to the patient's wellbeing, or if the patient is unable to comply with the requirements of the protocol, the patient will be removed from the study. In this event, the reason(s) for withdrawal will be documented.
- There is concurrent illness or other reasons that would, in the opinion of the investigator, affect assessment of clinical status or conduct of the study to a significant degree.
- The patient chooses to discontinue follow-up.

The reason(s) for study withdrawal will be documented. The reason(s) for withdrawing the patient from the treatment portion of the study will be documented in the case report form. If available, the following information will be recorded in the case report form: date of disease relapse, date of death, cause of death, and autopsy report.

5.10 Correlative studies

The correlative objective for this trial is to determine whether expression levels of inflammatory cytokines are regulated by miRNAs in patients with AML.

5.10.1 Specimen collection: The study participants will be offered to optionally co-enroll in IRB 156-95-FB for correlative study sample collection and biobanking. IRB 156-95-FB is the hematologic malignancies tissue bank that collects and stores tissues from patients with hematologic malignancies. Please see IRB 156-95-FB for further details.

5.10.2 Cytokine analysis: We will measure levels of inflammatory cytokines including IL-6, IL-1, IL-2, IL-8, TNF-α, GM-CSF, and CRP in serum obtained at diagnosis.

5.10.3 miRNA Experiments: We will develop cytokine-miRNA profile by utilizing patient samples of known gene sets/pathways. We will determine miRNA signature in patients' plasma. On the basis of pathway predictions combined with expression profile analysis, and bioinformatic approaches, we will determine the network of various miRNAs that regulate levels of inflammatory cytokines.

Further details about cytokine analysis and miRNA experiments are provided in the laboratory manual.

6.0 Measurement of Effect:

6.1 Response criteria: Response criteria and disease progression will be based on definitions provided by the International Working Group (Appendix E).(88) However, prior studies have demonstrated that multiple cycles of low-intensity therapy such as hypomethylating agent may be required to achieve complete remission. (25, 36-40) Hence, patients treated with low-intensity therapy may undergo restaging after multiple cycles. The number of cycles of hypomethylating agent used prior to restaging will be left to the discretion of the treating physician.

6.2 90-day mortality: Mortality from any causes within the first 90 days from the time of diagnosis will count towards 90-day mortality.

6.3 Percentage of patients proceeding to transplant: This will be calculated as the number of patients undergoing transplant divided by a total number of patients receiving either intensive or low intensity therapy.

6.4 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.

6.5 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,(48) and will be utilized to assess quality of life. For non-English speaking patients, any available validated translation (such as Spanish version(89, 90)) may be utilized. If no validated translation is available, an interpreter will be utilized if needed.

6.6 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.(80) For non-English speaking patients, any available validated translation (such as MOCA in Spanish (91, 92)) may be utilized. If no validated translation is available, an interpreter will be utilized if needed.

7.0 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**	**Survival data**
History and Physical Exam	X				Survival, disease status and transplant data will be recorded every 3 months for up to 2 years in alive patients
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	
CMET including albumin	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]			

Correlative study sample collection and biobanking	Patients will be offered to optionally co-enroll in IRB 156-95-FB for biobanking

BMI body mass index; CBC complete blood count; CMET Comprehensive metabolic panel (includes sodium, potassium, chloride, bicarbonate, creatinine, BUN, AST, ALT, total protein, albumin, bilirubin, alkaline phosphatase, calcium, glucose);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. Please see section 9.0 for AE reporting details.
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.

8.0 Drug Formulation and Procurement:

8.1 Cytarabine

8.1.1 Mechanism of Action: Cytarabine inhibits DNA synthesis. Cytarabine gains entry into cells by a carrier process, and then must be converted to its active compound, aracytidine triphosphate. Cytarabine is a pyrimidine analog and is incorporated into DNA; however, the primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair. The degree of cytotoxicity correlates linearly with incorporation into DNA; therefore, incorporation into the DNA is responsible for drug activity and toxicity. Cytarabine is specific for the S phase of the cell cycle (blocks progression from the G1 to the S phase).

8.1.2 Clinical Formulation: Commercially available for injection as: 20 mg/mL (5 mL, 50 mL); 100 mg/mL (20 mL)

8.1.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.1.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.
Protect from light. Store intact vials of powder for reconstitution at 20°C to 25°C (68°F to 77°F); store intact vials of solution at 15°C to 30°C (59°F to 86°F).
Store in original container. Ph of solution in vial is 7.4. The vials bear an expiration date.

Powder for reconstitution: Reconstituted solutions should be stored at room temperature and used within 48 hours.
For IV infusion: Solutions for IV infusion diluted in D5W or NS are stable for 8 days at room temperature, although the manufacturer recommends administration as soon as possible after preparation.

Powder for reconstitution: Reconstitute with bacteriostatic water for injection (for standard-dose).

Intermittent IV infusion:
Further dilute the appropriate dose of the injection solution in 100—250 mL of 5% Dextrose injection, 5% Dextrose and 0.9% Sodium Chloride injection, 5% Dextrose and Lactated Ringer's injection, Ringer's injection, or lactated Ringer's injection.

Continuous IV infusion:
Further dilute the appropriate dose of the injection solution in 500—1000 mL 5% Dextrose injection, 5% Dextrose and 0.9% Sodium Chloride injection, 5% Dextrose and Lactated Ringer's injection, Ringer's injection, or lactated Ringer's injection.

8.1.5 Administration: Infuse standard dose therapy (100 to 200 mg/m2/day) as a continuous infusion. Infuse intermediate or high-dose therapy (1000-1500 mg/m^2/day) over 1 to 3 hours.

8.1.6 Clinical Pharmacology:
Distribution: V_d: 3 ± 11.9 L/kg; total body water; widely and rapidly since it enters the cells readily; crosses blood-brain barrier with CSF levels of 40% to 50% of plasma level
Protein binding: 13%
Metabolism: Primarily hepatic; metabolized by deoxycytidine kinase and other nucleotide kinases to aracytidine triphosphate (active); about 86% to 96% of dose is metabolized to inactive uracil arabinoside (ARA-U)
Half-life elimination: IV: Initial: 7 to 20 minutes; Terminal: 1 to 3 hours
Excretion: Urine (~80%; 90% as metabolite ARA-U) within 24 hours

8.1.7 Potential Drug Interactions:
CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*
Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

8.1.8 Drug toxicities

Frequency not defined.

Cardiovascular: Angina pectoris, chest pain, hepatic veno-occlusive disease (also called hepatic sinusoidal obstruction syndrome), local thrombophlebitis, pericarditis

Central nervous system: Aseptic meningitis, cerebral dysfunction, dizziness, headache, neuritis, neurotoxicity, paralysis (intrathecal and IV combination therapy), reversible posterior leukoencephalopathy syndrome

Dermatologic: Acute generalized exanthematous pustulosis, alopecia, dermal ulcer, ephelis, pruritus, skin rash, urticaria

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Abdominal pain, anal fissure, anal inflammation, anorexia, diarrhea, esophageal ulcer, esophagitis, increased serum amylase, increased serum lipase, intestinal necrosis, mucositis, nausea, pancreatitis, sore throat, toxic megacolon, vomiting

Genitourinary: Urinary retention

Hematologic & oncologic: Anemia, bone marrow depression, hemorrhage, leukopenia, megaloblastosis, neutropenia (onset: 1 to 7 days; nadir [biphasic]: 7 to 9 days and at 15 to 24 days; recovery [biphasic]: 9 to 12 days and at 24 to 34 days), reticulocytopenia, thrombocytopenia (onset: 5 days; nadir: 12 to 15 days; recovery 15 to 25 days)

Hepatic: Hepatic insufficiency, increased serum transaminases (acute), jaundice

Hypersensitivity: Allergic edema, anaphylaxis

Infection including Sepsis

Neuromuscular & skeletal: Rhabdomyolysis

Ophthalmic: Conjunctivitis

Renal: Renal insufficiency

Respiratory: Acute respiratory distress, dyspnea, interstitial pneumonitis

Miscellaneous: Drug toxicity (cytarabine syndrome; chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia, ostealgia), fever

Hypersensitivity: Anaphylaxis resulting in acute cardiopulmonary arrest has been reported (rare).

Tumor lysis syndrome and subsequent hyperuricemia may occur.

Adverse events associated with high-dose cytarabine

Cardiovascular: Cardiomegaly, cardiomyopathy (in combination with cyclophosphamide)

Central nervous system: Neurotoxicity (patients with renal impairment), coma, drowsiness, neurocerebellar toxicity, peripheral neuropathy (motor and sensory), personality changes
Dermatologic: Alopecia (complete), desquamation, skin rash (severe)
Gastrointestinal: Gastrointestinal ulcer, necrotizing enterocolitis, pancreatitis, peritonitis, pneumatosis cystoides intestinalis
Hepatic: Hepatic abscess, hepatic injury, hyperbilirubinemia
Infection including Sepsis
Ophthalmic: Corneal toxicity, hemorrhagic conjunctivitis
Respiratory: Acute respiratory distress, pulmonary edema. May present as severe dyspnea with a rapid onset and refractory hypoxia with diffuse pulmonary infiltrates, leading to respiratory failure; may be fatal.

8.2 Idarubicin

8.2.1 Mechanism of Action: Idarubicin inhibits DNA and RNA synthesis by intercalation between DNA base pairs and by steric obstruction. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA.

8.2.2 Clinical Formulation: Commercially available for injection as: 5 mg/5 mL (5 mL); 10 mg/10 mL (10 mL); 20 mg/20 mL (20 mL)

8.2.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.2.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.

Store intact vials of solution refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light.

May draw up 1 mg/mL solution into a syringe (for administration) or further dilute in NS or D_5W. The reconstituted solution is hypotonic and is stable for 72 hours at room temperature or 1 week under refrigeration.
8.2.5 Administration: Administer as slow injection over 10 to 15 minutes into a free-flowing IV solution of NS or D_5W

8.2.6 Clinical Pharmacology:
Distribution: V_{dss}: 1,500 L/m^2; extensive tissue binding; CSF
Protein binding: 94-97%
Metabolism: Hepatic to idarubicinol (active metabolite)
Half-life elimination:
22 hours (range: 4 to 48 hours); >45 hours (idarubicinol)
Excretion: Primarily biliary; urine (8 to 10% as idarubicinol, ~2 to 5% as unchanged drug

8.2.7 Potential Drug Interactions:

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). Antineoplastic Agents (Anthracycline, Systemic) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

8.2.8 Drug toxicities

Frequency >10%:

Cardiovascular: Cardiac failure (dose-related), ECG abnormalities (transient; includes atrial premature contractions, S-T wave changes, supraventricular tachycardia, ventricular premature contractions; generally asymptomatic and self-limiting)

Central nervous system: Headache

Dermatologic: Alopecia (25% to 30%), skin rash (11%), urticaria

Gastrointestinal: Vomiting (30% to 60%), gastrointestinal hemorrhage (30%), diarrhea (9% to 22%), stomatitis (11%), nausea

Genitourinary: Urine discoloration (darker yellow)

Hematologic & oncologic: Anemia, bone marrow suppression (nadir: 10 to 15 days; recovery: 21 to 28 days; primarily leukopenia, thrombocytopenia

Hepatic: Increased serum bilirubin, increased serum transaminases

Miscellaneous: Radiation recall phenomenon

Frequency 1% to 10%:

Central nervous system: Peripheral neuropathy, seizure

Frequency <1% (Limited to important or life-threatening): Cardiomyopathy, hyperuricemia, myocarditis, typhlitis (neutropenic)

Miscellaneous toxicities- Vesicant; may cause severe local tissue damage and necrosis if extravasation occurs.

8.3 CPX-351 (liposomal preparation of daunorubicin and cytarabine)

8.3.1 Mechanism of Action: Liposomal preparation of daunorubicin (anthracycline) and cytarabine. Daunorubicin inhibits DNA and RNA synthesis by intercalation between DNA base pairs and by steric obstruction. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Cytarabine is a pyrimidine analog and is incorporated into DNA; however, the primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair.

8.3.2 Clinical Formulation: Commercially available for injection as: 44 mg daunorubicin and 100 mg cytarabine encapsulated in liposomes as a lyophilized cake in a single-dose vial for reconstitution.

8.3.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.3.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.

Calculate the dose based on daunorubicin and individual patient's BSA. Calculate the number of vials based on the daunorubicin dose. Remove the appropriate number of vials from the refrigerator and equilibrate to the room temperature for 30 minutes. Then, reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe and immediately thereafter start a 5-minute timer. Carefully swirl the contents of the vial for 5 minutes while gently inverting the vial every 30 seconds. After reconstitution, let rest for 15 minutes. The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates. After reconstitution (but before final dilution), each mL will contain 2.2 mg of daunorubicin and 5 mg of cytarabine. Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution. If the reconstituted product is not diluted into an infusion bag immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours. Aseptically withdraw the calculated volume of the reconstituted product from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. There may be residual product remaining in the vial. Discard unused portion. Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates. If the diluted infusion solution is not used immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only solutions without visible particles should be used.

8.3.5 Administration: infuse over 90 minutes.

8.3.6 Clinical Pharmacology:

Distribution: Daunorubicin 6.6 L; Cytarabine 7.1 L

Metabolism: Upon release from the liposomes, daunorubicin is catalyzed by aldoketo reductase and carbonyl reductase to daunorubicinol (active metabolite); cytarabine is metabolized by cytidine deaminase to Ara-U (inactive metabolite).

Half-life elimination: 31.5 hours (daunorubicin); 40.4 hours (cytarabine) with >99% of drug(s) remaining encapsulated in the liposomes

Excretion: Urine (9% daunorubicin; 71% cytarabine and Ara-U)

8.3.7 Potential Drug Interactions:

Cardiac Glycosides: May diminish the cardiotoxic effect of Anthracyclines. Anthracyclines may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Clozapine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Vaccines (Inactivated): May diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. *Risk D: Consider therapy modification*

Vaccines (Live): May enhance the adverse/toxic effect of Vaccines (Live). May diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines. *Risk X: Avoid combination*

8.3.8 Drug toxicities

Frequency >10%:
Cardiovascular: Edema (51%), cardiac arrhythmia (30%), cardiotoxicity (20%), hypotension (20%), hypertension (18%), chest pain (17%)
Central nervous system: Headache (33%), fatigue (32%), sleep disorder (25%), chills (23%), dizziness (18%), delirium (16%), anxiety (14%)
Dermatologic: Skin rash (54%), pruritus (15%)
Endocrine & metabolic: Hyponatremia (grades 3/4: 6% to 14%)
Gastrointestinal: Diarrhea (≤66%), nausea (47%), colitis (≤45%), mucositis (44%), constipation (40%), abdominal pain (33%), decreased appetite (29%), vomiting (24%), hemorrhoids (11%)
Hematologic & oncologic: Anemia (100%), neutropenia (100%; grade 4 [prolonged]: 10% to 17%), thrombocytopenia (100%; grade 3 [prolonged]: 25% to 28%), hemorrhage (70%; grades 3 to 5: 10%), febrile neutropenia (68%; grades 3 to 5: 66%), petechia (11%)
Hypersensitivity: Transfusion reaction (11%)
Infection including Bacteremia (24%), fungal infection (18%), sepsis (11%)

Local: Injection site reaction (16%; includes catheter and device site)
Neuromuscular & skeletal: Musculoskeletal pain (38%)
Ophthalmic: Visual impairment (11%)
Renal: Renal insufficiency (11%)
Respiratory: Cough (33%), dyspnea (32%), pneumonia (26%), hypoxia (18%), upper respiratory tract infection (18%), pleural effusion (16%)
Miscellaneous: Fever (17%)

Frequency 1% to 10%:
Central nervous system: Hallucination (<10%)
Endocrine & metabolic: Hypokalemia (grades 3/4: 6% to 9%), hypoalbuminemia (grades 3/4: 2% to 7%), abnormal alanine aminotransferase (grades 3/4: ≤5%)
Gastrointestinal: Dyspepsia (<10%)
Hepatic: Hyperbilirubinemia (grades 3/4: 2% to 6%)
Ophthalmic: Conjunctivitis (<10%), dry eye syndrome (<10%), eye irritation (<10%), eye pain (<10%), injected sclera (<10%), ocular hyperemia (<10%), periorbital edema (<10%), swelling of eye (<10%)
Otic: Deafness (<10%)
Respiratory: Pneumonitis (<10%)

8.4 Decitabine

8.4.1 Mechanism of Action: After phosphorylation, decitabine is incorporated into DNA and inhibits DNA methyltransferase causing hypomethylation and subsequent cell death (within the S-phase of the cell cycle).

8.4.2 Clinical Formulation: Commercially available for injection as 50 mg single use vial.

8.4.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.4.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.

Store intact vials at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Solutions diluted for infusion in NS or D5W may be stored for up to 4 hours prior to infusion refrigerated at 2°C to 8°C (36°F to 46°F) if prepared with cold infusion fluids. Infusion should begin within 15 minutes of preparation if room temperature infusion solutions are utilized.

8.4.5 Administration: infuse over 1 to 3 hours.

8.4.6 Clinical Pharmacology:
Distribution: ~63 to 89 L/m^2
Metabolism: Possibly via deamination by cytidine deaminase
Half-life elimination: ~30 to 35 minutes

8.4.7 Potential Drug Interactions:

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

8.4.8 Drug toxicities

Frequency >10%:

Cardiovascular: Peripheral edema (25% to 27%), edema (5% to 18%), heart murmur (16%), hypotension (6% to 11%)

Central nervous system: Fatigue (46%), headache (23% to 28%), insomnia (14% to 28%), rigors (22%), dizziness (18% to 21%), chills (16%), pain (5% to 13%), confusion (8% to 12%), lethargy (12%), hypoesthesia (11%), anxiety (9% to 11%)

Dermatologic: Pallor (23%), skin rash (11% to 19%), erythema (5% to 14%), cellulitis (9% to 12%), pruritus (9% to 11%)

Endocrine & metabolic: Hyperglycemia (6% to 33%), hypoalbuminemia (7% to 24%), hypomagnesemia (5% to 24%), hypokalemia (12% to 22%), hyponatremia (19%), hyperkalemia (13%)

Gastrointestinal: Nausea (40% to 42%), constipation (30% to 35%), diarrhea (28% to 34%), vomiting (16% to 25%), anorexia (≤8% to 23%), decreased appetite (≤8% to 23%), abdominal pain (5% to 14%), stomatitis (11% to 12%), dyspepsia (10% to 12%)

Hematologic & oncologic: Neutropenia (38% to 90%; grades 3/4: 37% to 87%; recovery 28 to 50 days), thrombocytopenia (27% to 89%; grades 3/4: 24% to 85%), anemia (31% to 82%; grades 3/4: 22%), petechia (12% to 39%), febrile neutropenia (20% to 29%; grades 3/4: 23%), leukopenia (6% to 28%; grades 3/4: 22%), bruise (9% to 22%), oral mucosal petechiae (13%), lymphadenopathy (12%)

Hepatic: Hyperbilirubinemia (6% to 14%), increased serum alkaline phosphatase (11%)

Local: Localized tenderness (11%)

Neuromuscular & skeletal: Arthralgia (17% to 20%), limb pain (18% to 19%), back pain (17% to 18%), weakness (15%)

Respiratory: Cough (27% to 40%), dyspnea (29%), pneumonia (20% to 22%), pharyngitis (16%), rales (8% to 14%), epistaxis (13%)

Miscellaneous: Fever (6% to 53%)

Frequency 5% to 10%:

Cardiovascular: Tachycardia (8%), chest wall pain (7%), chest pain (≤6% to 7%), chest discomfort (≤6% to 7%), facial edema (6%), hypertension (6%), cardiac failure (5%)

Central nervous system: Depression (9%), falling (8%), malaise (5%), mouth pain (5%)

Dermatologic: Alopecia (8%), xeroderma (8%), urticaria (6%), catheter site erythema (5%), night sweats (5%)

Endocrine & metabolic: Hyperuricemia (10%), weight loss (9%), increased lactate dehydrogenase (8%), dehydration (6% to 8%), hypochloremia (6%), increased serum bicarbonate (6%), decreased serum bicarbonate (5%), hypoproteinemia (5%)

Gastrointestinal: Mucosal inflammation (9%), gingival hemorrhage (8%), hemorrhoids (8%), loose stools (7%), tongue ulcer (7%), oral candidiasis (6%), toothache (6%),

dysphagia (5% to 6%), abdominal distention (5%), gastroesophageal reflux disease (5%), glossalgia (5%), oral mucosa ulcer (lip: 5%)
Genitourinary: Urinary tract infection (7%), dysuria (6%)
Hematologic & oncologic: Hematoma (5%), pancytopenia (5%), thrombocythemia (5%)
Hepatic: Ascites (10%), increased serum AST (10%), decreased serum bilirubin (5%)
Hypersensitivity: Transfusion reaction (7%)
Infection including Candidiasis (10%), bacteremia (5% to 8%), staphylococcal infection (7%), tooth abscess (5%)
Local: Catheter infection (8%), catheter pain (5%), swelling at injection site (5%)
Neuromuscular & skeletal: Myalgia (5% to 9%), muscle spasm (7%), ostealgia (6%), musculoskeletal discomfort (≤5% to 6%), musculoskeletal pain (≤5% to 6%), crepitations (5%)
Ophthalmic: Blurred vision (6%)
Otic: Otalgia (6%)
Renal: Polyuria (5%)
Respiratory: Hypoxia (10%), upper respiratory tract infection (10%), abnormal breath sounds (5% to 10%), pharyngolaryngeal pain (8%), pulmonary edema (6%), sinusitis (5% to 6%), pleural effusion (5%), post nasal drip (5%), sinus congestion (5%)

Frequency <5% (Limited to important or life-threatening): Abscess (peridiverticular), acute cardiorespiratory failure, anaphylaxis, atrial fibrillation, cardiomyopathy, catheter site hemorrhage, cholecystitis, fungal infection, gastrointestinal hemorrhage, gingival pain, hemoptysis, hypersensitivity reaction, intracranial hemorrhage, mental status change, myocardial infarction, mycobacterium avium complex, pseudomonal lung infection, pulmonary aspergillosis, pulmonary embolism, pulmonary infiltrates, pulmonary mass, renal failure, sepsis, splenomegaly, supraventricular tachycardia, Sweet's syndrome (acute febrile neutrophilic dermatosis), urethral bleeding

8.5 Azacitidine

8.5.1 Mechanism of Action: Azacitidine inhibits DNA methyltransferase causing hypomethylation and subsequent cell death (within the S-phase of the cell cycle).

8.5.2 Clinical Formulation: Commercially available for injection as 100 mg vial.

8.5.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.5.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.
Infusion must be completed within 1 hour of (vial) reconstitution.
Wash with soap and water if azacitidine suspension comes in contact with the skin.

8.5.5 Administration: infuse over 10 to 40 min.

8.5.6 Clinical Pharmacology:

Distribution: 76 ± 26 L; does not cross blood-brain barrier
Metabolism: Hepatic; hydrolysis to several metabolites
Half-life elimination: IV: ~4 hours
Excretion: Urine (50% to 85%); feces (<1%)

8.5.7 Potential Drug Interactions:

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*
Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

8.5.8 Drug toxicities

Frequency >10%:

Cardiovascular: Peripheral edema (7% to 19%), chest pain (16%)
Central nervous system: Fatigue (13% to 36%), rigors (26%), headache (22%), dizziness (19%), anxiety (5% to 13%), depression (12%), malaise (11%), pain (11%), insomnia (9% to 11%)
Dermatologic: Erythema (7% to 17%), pallor (16%), skin lesion (15%), skin rash (10% to 14%), pruritus (12%), diaphoresis (11%)
Endocrine & metabolic: Weight loss (≤16%), pitting edema (15%), hypokalemia (6% to 13%)
Gastrointestinal: Nausea (48% to 71%), vomiting (27% to 54%), constipation (34% to 50%), diarrhea (36%), anorexia (13% to 21%), abdominal pain (11% to 16%), abdominal tenderness (12%)
Hematologic & oncologic: Thrombocytopenia (66% to 70%; grades 3/4: 58%), anemia (51% to 70%; grades 3/4: 14%), neutropenia (32% to 66%; grades 3/4: 61%), leukopenia (18% to 48%; grades 3/4: 15%), bruise (19% to 31%), petechia (11% to 24%), febrile neutropenia (14% to 16%; grades 3/4: 13%), bone marrow depression (nadir: days 10 to 17; recovery: days 28 to 31)
Local: Injection site reactions (14% to 29%): Erythema (35% to 43%; more common with IV administration), pain (19% to 23%; more common with IV administration), bruising (5% to 14%)
Neuromuscular & skeletal: Weakness (29%), arthralgia (22%), limb pain (20%), back pain (19%), myalgia (16%)
Respiratory: Cough (11% to 30%), dyspnea (5% to 29%), pharyngitis (20%), epistaxis (16%), nasopharyngitis (15%), upper respiratory infection (9% to 13%), pneumonia (11%), rales (9% to 11%)
Miscellaneous: Fever (30% to 52%)

Frequency 5% to 10%:

Cardiovascular: Heart murmur (10%), tachycardia (9%), hypertension (≤9%), hypotension (7%), syncope (6%), chest wall pain (5%)
Central nervous system: Lethargy (7% to 8%), hypoesthesia (5%), postoperative pain (5%)
Dermatologic: Night sweats (9%), cellulitis (8%), rash at injection site (6%), urticaria (6%), skin nodules (5%), xeroderma (5%)

Gastrointestinal: Gingival hemorrhage (10%), stomatitis (8%), hemorrhoids (7%), dyspepsia (6% to 7%), abdominal distention (6%), loose stools (6%), dysphagia (5%), tongue ulcer (5%)
Genitourinary: Urinary tract infection (8% to 9%), dysuria (8%), hematuria (≤6%)
Hematologic & oncologic: Lymphadenopathy (10%), hematoma (9%), oral mucosal petechiae (8%), postprocedural hemorrhage (6%), oral hemorrhage (5%)
Hypersensitivity: Transfusion reaction (7%)
Infection: Herpes simplex infection (9%)
Local: Itching at injection site (7%), hematoma at injection site (6%), induration at injection site (5%), injection site granuloma (5%), skin discoloration at injection site (5%), swelling at injection site (5%)
Neuromuscular & skeletal: Muscle cramps (6%)
Respiratory: Rhinorrhea (10%), wheezing (9%), abnormal breath sounds (8%), nasal congestion (6%), pharyngolaryngeal pain (6%), pleural effusion (6%), post nasal drip (6%), rhinitis (6%), rhonchi (6%), atelectasis (5%), sinusitis (5%)
Miscellaneous: Lymphadenopathy (10%), herpes simplex (9%), night sweats (9%), transfusion reaction (7%), mouth hemorrhage (5%)

Frequency <5%, postmarketing, and/or case reports: Abscess (limb, perirectal), aggravated bone pain, agranulocytosis, anaphylactic shock, atrial fibrillation, azotemia, bacterial infection, blastomycosis, bone marrow failure, cardiac failure, catheter site hemorrhage, cellulitis, cerebral hemorrhage, cholecystectomy, cholecystitis, congestive cardiomyopathy, decreased serum bicarbonate, dehydration, diverticulitis, fibrosis (interstitial and alveolar), gastrointestinal hemorrhage, glycosuria, hemophthalmos, hemoptysis, hepatic coma, hypersensitivity reaction, hypophosphatemia, increased serum creatinine, injection site infection, interstitial pulmonary disease, intracranial hemorrhage, leukemia cutis, melena, necrotizing fasciitis, neutropenic sepsis, orthostatic hypotension, pancytopenia, pneumonitis, polyuria, pulmonary infiltrates, pyoderma gangrenosum, renal failure, renal tubular acidosis, respiratory distress, seizure, sepsis, sepsis syndrome, septic shock, splenomegaly, Sweet's syndrome, tissue necrosis at injection site, toxoplasmosis, tumor lysis syndrome

8.6 Venetoclax

8.6.1 Mechanism of Action: Venetoclax is a potent, selective, orally bioavailable small-molecule inhibitor of BCL-2.

8.6.2 Clinical Formulation: Commercially available as 10, 50 and 100 mg tablets.

8.6.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.6.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.

Store at or below 30°C (86°F).

8.6.5 Administration:

Swallow the whole tablet with a meal. Do not crush, chew, or break.

8.6.6 Clinical Pharmacology:

Distribution: 256 to 321 L
Metabolism: Hepatic, predominantly via CYP3A4/5; the major metabolite is M27 (has BCL-2 inhibitory activity)
Half-life, elimination: ~26 hours
Time to peak: 5 to 8 hours
Excretion: Feces (>99.9%; ~21% as unchanged drug); Urine (<0.1%)

8.6.7 Potential Drug Interactions:

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*
CYP3A4 Inducers (Moderate): May decrease the serum concentration of Venetoclax. *Risk X: Avoid combination*
CYP3A4 Inducers (Strong): May decrease the serum concentration of Venetoclax. *Risk X: Avoid combination*
CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Venetoclax. Management: Reduce the venetoclax dose by at least 50% in patients requiring these combinations. *Risk D: Consider therapy modification*
CYP3A4 Inhibitors (Strong): May increase the serum concentration of Venetoclax. Management: These combinations are contraindicated during venetoclax initiation and ramp-up. In patients receiving steady venetoclax doses after completing ramp-up, reduce the venetoclax by at least 75% if strong CYP3A4 inhibitor use cannot be avoided. *Risk D: Consider therapy modification*
Deferasirox: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*
Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*
Grapefruit Juice: May increase the serum concentration of Venetoclax. *Risk X: Avoid combination*
Vaccines (Inactivated): Venetoclax may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*
Vaccines (Live): Venetoclax may enhance the adverse/toxic effect of Vaccines (Live). Venetoclax may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live, attenuated vaccines before, during, or after (prior to B-cell recovery) venetoclax treatment. *Risk X: Avoid combination*
Warfarin: Venetoclax may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

8.6.8 Drug toxicities

Frequency generally >10%:

Blood and lymphatic system disorders: Thrombocytopenia, Leucopenia, Lymphopenia, Neutropenia, Febrile neutropenia, Anemia, Pancytopenia
Gastrointestinal disorders: Nausea, Diarrhea, Constipation, Vomiting, Abdominal pain, decreased appetite, mucositis, proctitis
General disorders and administration site conditions: Peripheral edema, fatigue, pyrexia, cachexia
Multiple organ dysfunction syndrome, respiratory failure
Infections and infestations: Pneumonia, Sepsis, Urinary tract infection, cellulitis, localized infection, Device related infection, Upper respiratory tract infection, lower respiratory tract infection, candida infection, bacteremia, mucosal infection
Musculoskeletal and connective tissue disorders: Back pain, myalgia or musculoskeletal pain, arthralgia
Nervous system disorders: Dizziness
Skin and subcutaneous tissue disorders: Rash
Respiratory, thoracic and mediastinal disorders: Cough, hypoxia, oropharyngeal pain, dyspnea
Other: Hemorrhage, gastrointestinal hemorrhage, hypotension, hypertension, headache, pruritus

Laboratory abnormalities, Hyperglycemia, hypocalcemia, hypoalbuminemia, hypokalemia, hyponatremia, hypophosphatemia, hyperphosphatemia, hyperbilirubinemia, hypomagnesemia, Blood creatinine increased, blood bicarbonate decreased, hyperkalemia, hyperphosphatemia, Increased serum aspartate aminotransferase or alanine aminotransferase

Tumor lysis syndrome (3%) including hyperuricemia

8.7 Glasdegib

8.7.1 Mechanism of Action: Glasdegib binds to and inhibits Smoothened (SMO), a transmembrane protein involved in hedgehog signal transduction.

8.7.2 Clinical Formulation: Commercially available as 25 mg and 100 mg tablets.

8.7.3 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.7.4 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

8.7.5 Administration: Swallow whole tablets without splitting or crushing the tablets.

8.7.6 Clinical Pharmacology:

Distribution: 188 L
Metabolism: Primarily hepatic via CYP3A4, with minor contributions by CYP2C8 and UGT1A9
Half-life elimination: 17.4 hours ± 3.7 hours
Time to peak: 1.3 to 1.8 hours
Excretion: Urine: 49% (17% as unchanged drug); Feces: 42% (20% as unchanged drug)

8.7.7 Potential Drug Interactions:

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*
CYP3A4 Inducers (Strong): May decrease the serum concentration of Glasdegib. *Risk X: Avoid combination*
CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*
CYP3A4 Inhibitors (Strong): May increase the serum concentration of Glasdegib. Management: Consider alternatives to this combination when possible. If the combination must be used, monitor closely for evidence of QT interval prolongation and other adverse reactions to glasdegib. *Risk D: Consider therapy modification*
Deferasirox: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*
QT-prolonging Agents (Highest Risk): QT-prolonging Agents (Indeterminate Risk - Avoid) may enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). *Risk C: Monitor therapy*

8.7.8 Drug toxicities

Frequency >10%:
Cardiovascular: Edema (30%), atrial arrhythmia (13%), chest pain (12%)
Central nervous system: Fatigue (36%), dizziness (18%), headache (12%)
Dermatologic: Skin rash (20%)
Endocrine & metabolic: Hyponatremia (11% to 54%), hypomagnesemia (33%), hyperkalemia (16%), hypokalemia (15%), weight loss (13%)
Gastrointestinal: Nausea (29%), decreased appetite (21%), dysgeusia (21%), mucositis (21%; grade ≥3: 1%), constipation (20%), abdominal pain (19%), diarrhea (18%), vomiting (18%)
Hematologic & oncologic: Anemia (43%; grade ≥3: 41%), hemorrhage (36%; grade ≥3: 6%), febrile neutropenia (31%; grade ≥3: 31%), thrombocytopenia (30%; grade ≥3: 30%), decreased white blood cell count (11%; grade ≥3: 11%)
Hepatic: Increased serum aspartate aminotransferase (28%), increased serum bilirubin (25%), increased serum alanine aminotransferase (24%), increased serum alkaline phosphatase (23%)
Neuromuscular & skeletal: Musculoskeletal pain (30%), increased creatine phosphokinase in blood specimen (16%), muscle spasm (15%)
Renal: Increased serum creatinine (96%), renal insufficiency (19%)
Respiratory: Dyspnea (23%), pneumonia (19%), cough (18%)
Miscellaneous: Fever (18%)

Frequency 1% to 10%:
Cardiovascular: Prolonged QT interval on ECG (4% to 5%)
Infection: Sepsis (7%)

Frequency not defined: Endocrine & metabolic: Hypophosphatemia

Section 9.0 Toxicity and Adverse Event Reporting Guidelines:

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

The reporting is only for "study drug," from the time of initiation of study drug until 30 days after last administration of study medication, or in case of low intensity therapy, 30 days after the end of 3rd cycle or last cycle (if stopped prior to the 3rd cycle) of venetoclax-hypomethylating combination or low-intensity therapy. Adverse event and serious adverse events will be followed until baseline, ≤ grade 1 levels, death, or until no further improvement is reasonably expected. Toxicity will be assessed using the revised NCI CTCAE version 4.03 (Appendix F).
Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC DSMC.

9.1 Definitions:
9.1.1 Adverse Event
An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.,* the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, require dose modifications and/or if the investigator considers them to be adverse events.

9.1.2 Treatment-emergent Adverse Event
Treatment-emergent adverse event is defined as any adverse event with onset or worsening from the time that the first dose of study drug is administered until 30 days after the final dose of study

drug is administered, or in case of low intensity therapy, 30 days after the end of 6th cycle or last cycle (if stopped prior to the 6th cycle) of decitabine therapy.

9.1.3 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

9.1.4 Serious Adverse Event

A serious adverse event is one that at any dose (including overdose) and regardless of causality:

- Results in death
- Is a serious threat to life, health, safety or welfare-fare of subject[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Requires intervention to prevent permanent impairment or damage
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is another serious important medical event[3]
- Is any medical event in an investigational drug study that requires treatment to prevent one of the outcomes listed above
- Seriously jeopardizes the rights, safety, or welfare of subjects

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.2 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC)

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

9.2.1 IRB REPORTING

All internal adverse events (AEs) must be reported to the local IRB promptly per institutional human research protection program policies.

9.2.2 FRED & PAMELA BUFFETT CANCER CENTER DATA AND SAFETY MONITORING COMMITTEE (DSMC) REPORTING

Grade 4 anemia, thrombocytopenia, neutropenia and leucopenia are routinely expected for almost all patients receiving chemotherapy for leukemia; these events will not be included in routine reports to the UNMC DSMC. All other adverse events grade 3 or higher (expected or unexpected, at least possibly related to the study drug) will be reported to the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) in accordance with the DSMC guidelines. The consenting investigator or the site principal investigator will make a determination of whether a grade ≥3 toxicity is related to the study drug.
Deaths occurring within 30 days of the study drug regardless of relationship will be reported to the UNMC DSMC.
Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.
Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.
Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.
Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.
Definitely related: The occurrence and timing of the AE are clearly attributable to the study treatment.

The reporting is only for the "study drug," from the time of initiation of study drug until 30 days after last administration of the study drug, or in case of low intensity therapy, 30 days after the end of 3rd cycle or last cycle (if stopped prior to the 3rd cycle) of venetoclax-hypomethylating combination or other low-intensity therapy. The "study drug" refers to the chemotherapy regimen planned at the time of initiation of the first cycle of therapy. Addition of a new agent, unless pre-planned at the time of initiation of the first cycle of therapy, will constitute a change in therapy.

All AEs will be followed until baseline, ≤ grade 1 levels, death, or until no further improvement is reasonably expected. AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 30 days after the final dose of the study drug.

Copies of the AE report will be submitted to the IRB as indicated in Section 9.2.1. Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

9.3 Monitoring

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee will review this protocol on at least an annual basis. In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per the DSMC policy. All adverse events and toxicity reporting will be reported to the UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

Various methods will be implemented by the sponsor (UNMC) to exchange information with participating sites:

- Site Initiation/Orientation
- Regular Teleconferences including group wide progress within the agenda
- Investigator meetings as feasible (remote or on an as needed basis, possibly in conjunction with larger meetings)
- Email distributions/reports as needed

9.3.1 Data Monitoring

For this study, data monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s). Monitoring is a Quality Control, continuous process during the entire trial.

All participating sites will perform routine data monitoring for this study by each site's institution according to the institution's internal guidelines and policies. A copy of the site's monitoring report will be submitted to UNMC project coordinator.

9.4 Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance**,** one point process during the trial.

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo audit on at least a quarterly basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at:
https://www.unmc.edu/cancercenter/clinical/prms.html.

Section 10.0 Statistical Considerations:

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

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

10.3 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).

10.4 Sample size justification: An optimal Simon two-stage design (93) 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(94) software was used to conduct all sample size analyses.

10.5 Data Analysis:

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(95) 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 90-day mortality will be explored using a chi-square test (95). The proportion (and associated 95% confidence interval) of patients with impairments across various domains of geriatric assessment will be presented.

10.6 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. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

10.7 Efficacy endpoints

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 (OS)
OS 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 distribution. OS rates at 1 and 2 years will be provided as well as 95% CI.

Proportion transplanted
Included in this comparison are all patients who are enrolled in this study. The percentage of patients proceeding to transplant will be calculated for the lower intensity and intensive therapy groups along with 95% CI. Groups will be compared with chi-square tests.

Exploratory endpoints and correlative studies
Descriptive statistics will be used to compare patient characteristics between groups. Mean, standard deviation (SD), median and range will be reported for continuous variables, and they will be compared with t-tests or Wilcoxon rank sum test. Frequencies and percentages will be used to describe categorical variables, and they will be compared between groups with chi-square tests.

10.8 Estimated duration of study and accrual goal
It is expected that 15-20 patients will be enrolled in the trial each year. To meet the accrual goals of 75, we require approximately 4-5 years. After accrual is met, we plan to follow the patients for up to an additional 2 years to assess survival endpoints.

10.9 Stopping rule
The therapies used in this study are considered standard of care. A risk stratification strategy is considered necessary for therapy allocation even outside of a clinical trial. Significant toxicities are frequently observed in clinical practice in this patient population. For example, in one study with venetoclax in combination with hypomethylating agent, serious adverse reactions were reported in 75-85% of patients.(14, 15)

With this background, the proposed two-stage design (93) 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 DSMC 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. For the purpose of stopping rules, patients will be considered evaluable if they receive at least one dose of study medication and if alive, maintain study follow-up for at least one month after enrolling to the study.

11.0 Records to be Kept:
Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. See attached Data forms.

Serious adverse events, when noted, will be recorded on site via the standard serious adverse events form.

11.1 Quality assurance: Complete records must be maintained in a research chart on each patient treated on the protocol. These records should include primary documentation (e.g., lab. report slips, imaging reports, pathology reports, physician notes, etc.) which confirm that:
- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (bone marrow biopsy, lab reports, dated notes on clinical assessment, as appropriate).

11.2 Electronic Data Capturing (EDC) System
For investigator –initiated trials at UNMC, we will be utilizing Forte EDC application. Data will be stored electronically for this study on the Forte secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Forte logo.

Forte provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Forte through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

12.0 Patient Consent:

12.1 Human Subjects Research Protection Training
All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population
Patients are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material
Pathology material must be reviewed, and the diagnosis confirmed by University Nebraska Medical Center pathology department (retrospectively).

12.4 Recruitment and Informed Consent
Patients with an initial diagnosis of AML seen and evaluated at Nebraska Medicine or IRB approved participating sites will be available for recruitment. These patients will be informed of

the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed below.

National Library of Medicine - http://clinicaltrials.gov (NCT03226418)
National Cancer Institute - http://www.cancer.gov (NCI-2017-01285)

12.5 Subject Competency
Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigator judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent
If the patient chooses to be a participant in this study, informed consent will be obtained by the investigator. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension
When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld.
The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects
It is hoped that the use of risk-stratified therapy allocation may result in lower early mortality rate or lower rates of other toxicities.

12.10 Potential Benefits to Society.
Information obtained from this study may help other cancer patients by contributing to the knowledge of whether the proposed risk-stratified therapy allocation offers potential advantages over other strategies currently available.

12.11 Potential Risks
The use of cytotoxic chemotherapy is associated with numerous potential risks. Chemotherapy is considered to be a valid treatment option for patients with AML. Chemotherapy utilized in this study are in fact considered standard of care at UNMC and many other cancer centers in the United States. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment that might consist of other chemotherapy drugs given alone or in combination.

12.12 Therapeutic Alternatives
If patients choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include similar or other chemotherapy drugs given alone or in combination.

12.13 Risk/Benefit Relationship
Although there are inherent risks involved because of the use of chemotherapy agents, the risk is considered to be acceptable in the setting of cancer given the potential benefit of chemotherapy in extending survival or improving quality of life over time.

12.14 Consent Form Documents
No information will be purposely withheld from the patients. The consent document used in this study will include the adult consent document. See attached consent form

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14.0 Data Collection Forms:
Attached

Appendix A. 2017 ELN risk stratification by genetics*

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low}† Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{high}† Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡ Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type NPM1 and FLT3-ITD^{high}† Mutated RUNX1⁋ Mutated ASXL1⁋ Mutated TP53#

†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5)
‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.
‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
⁋These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
#TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

*In our study, we will use the results of conventional karyotyping/fluorescence in situ hybridization (FISH) for classification of risk categories since molecular mutation panel generally take more than 7-10 days to results, however, if certain molecular mutation results (e.g. NPM1 and FLT3 ITD mutations) are available at the time of risk categorization and decision-making regarding low intensity and intensive chemotherapy, the results will be taken into consideration. Since allelic ratio is not performed in routine practice, if FLT3 ITD is present, patients will be categorized as intermediate risk category. If cytogenetic and/or FISH testing cannot be performed despite reasonable attempt because of reasons such as failure to grow cells/induce mitosis, lack of suitable specimens, patients will be categorized as intermediate-risk AML. Enrollment of such cases should be discussed with the principal investigator.

Appendix B. AML with myelodysplasia-related changes

The presence of multilineage dysplasia alone will not classify a case as AML with myelodysplasia-related changes when a mutation of NPM1or biallelic mutation of CEBPA is present. In cases lacking these mutations, the morphologic detection of multilineage dysplasia (defined as the presence of 50% or more dysplastic cells in at least 2 cell lines) remains a poor prognostic indicator and is sufficient to make a diagnosis of AML with myelodysplasia-related changes. A history of MDS remains as an inclusion criterion for this category as does the presence of an MDS-related cytogenetic abnormality with 1 exception: del(9q) has been removed as a defining cytogenetic abnormality for AML with myelodysplasia-related changes because of its association with NPM1 or biallelic CEBPA mutations and its apparent lack of prognostic significance in those settings. The cytogenetic abnormalities that now define AML with myelodysplasia-related changes are listed below.

Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded

Cytogenetic abnormalities
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
−7/del(7q)
del(5q)/t(5q)
i(17q)/t(17p)
−13/del(13q)
del(11q)
del(12p)/t(12p)
idic(X)(q13)
Balanced abnormalities
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p36.3;q21.2)
t(2;11)(p21;q23.3)
t(5;12)(q32;p13.2)
t(5;7)(q32;q11.2)
t(5;17)(q32;p13.2)
t(5;10)(q32;q21.2)
t(3;5)(q25.3;q35.1)

Appendix C. Eligibility Checklist

Date Completed:	Protocol #: 179-17	Institution: UNMC	Patient ID:
Checklist version # 1.0		Waiver #:	

Eligibility Checklist	Yes	No	N/A	
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	[ ]	[ ]	[ ]	1.
2. Patients aged ≥60 years	[ ]	[ ]	[ ]	2.
3. Karnofsky Performance Status ≥60%	[ ]	[ ]	[ ]	3.
4. Subjects must able and willingly give signed informed consent	[ ]	[ ]	[ ]	4.
*All of the above must be **yes** to be eligible.*				
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.	[ ]	[ ]	[ ]	1.
2. Relapsed or refractory AML, who require salvage therapy	[ ]	[ ]	[ ]	2.
3. Prior exposure to decitabine or azacitidine will be an exclusion criterion for the use of decitabine or azacitidine alone.	[ ]	[ ]	[ ]	3.
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.	[ ]	[ ]	[ ]	4.
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	[ ]	[ ]	[ ]	5.
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.	[ ]	[ ]	[ ]	6.
7. Ejection fraction <45% will be an exclusion criteria for intensive chemotherapy. Such patients may receive low intensity therapy.	[ ]	[ ]	[ ]	7.
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	[ ]	[ ]	[ ]	8.

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. *All of the above must be **no** to be eligible.*	[ ] [ ] [ ] 9.

Eligibility: [ ] Patient satisfies all criteria.
[ ] Patient not formally eligible, but admitted to study because (state reason);

_____

_____

Patient Initials: _____MR #_____DOB _____

ELIGIBILITY reviewed and confirmed
Site Investigator Signature _____Date_____

APPENDIX D. Hematopoietic Cell Transplant Comorbidity Index

Comorbidity	Definition	Score
Arrythmia	Afib or flutter, sick sinus syndrome or ventricular arrhythmia	1
Cardiac	Coronary Artery Disease [1]), CHF, MI or EF < 50%	1
IBD	Crohns Disease or Ulcerative Colitis	1
Diabetes	Requiring treatment with insulin or oral agents	1
CVA	History of TIA or CVA	1
Psychiatric	Depression or anxiety requiring psychiatric consult or treatment	1
Mild Hepatic	Chronic hepatitis or bili > 1.3 but < 2.0 or AST > 46 but < 115 or ALT > 66 but < 165	1
Obesity	BMI > 35 kg/m2	1
Infection	Continuing antimicrobial treatment required after day 0	1
Rheumatologic	SLE, RA, polymyositis, MCTD, polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Renal	Creatinine > 2 mg/dL, dialysis or prior renal transplant	2
Mild pulmonary	DLCO or FEV1 66%-80% of predicted or dyspnea on slight activity	2
Prior tumor	Any prior solid malignancy except nonmelanoma skin cancer	3
Heart Valve	Any except mitral valve prolapse	3
Severe Pulmonary	DLCO and/or FEV1 ≤ 65% predicted or requiring O2	3
Severe Hepatic	Cirrhosis, bili > 2, AST > 115 or ALT > 165	3

[1]) CAD is defined as one or more vessel stenosis requiring medical therapy, stent placement, PTCA or bypass grafting

Many patients may not have undergone a pulmonary function test or an echocardiogram prior to enrollment. In the absence of a known diagnosis of chronic pulmonary obstructive disease or other pulmonary disease, or congestive heart failure, such patients will receive a score of 0 for pulmonary comorbidity and congestive heart failure. The use of prophylactic antibiotics or fevers thought to be possibly related to tumor fever may NOT be used to assign a score of 1 for infection. A prior diagnosis of solid or lymphoid malignancies but NOT myelodysplastic syndrome or other myeloid malignancies get a score of 3 for prior malignancy.
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. Please see section 5.1.1 for further details and clarification. Additional clarification may be obtained from the expert review paper by Sorror (71), who designed the tool.

APPENDIX E. Disease response and treatment failure criteria as per the international working group criteria

Response criteria

Response Criterion	Time of Assessment	Neutrophils (μL)	Platelets (μL)	Bone Marrow Blasts (%)
Early treatment assessment	7-10 days after therapy	NA	NA	< 5
Morphologic leukemia-free state	Varies by protocol	NA	NA	< 5
Morphologic CR	Varies by protocol	> 1,000	> 100,000	< 5
Cytogenetic CR	Varies by protocol	> 1,000	> 100,000	< 5
Molecular CR	Varies by protocol	> 1,000	> 100,000	< 5
Partial remission	Varies by protocol	> 1,000	> 100,000	> 50 or decrease to 5-25

Morphologic complete remission: A complete remission designation requires that the patient achieve the morphologic leukemia-free state and have an absolute neutrophil count of more than 1,000/microL and platelet count of ≥100,000/microL. Hemoglobin concentration or hematocrit has no bearing on remission status, although the patient must be independent of transfusions.

Molecular complete remission or minimal residual disease negative status: Molecular complete remission requires achievement of complete remission and absence of any detectable disease by molecular and/or multidimensional flow cytometric techniques.

Treatment failure

Category	Definition
Resistant disease	Patient survives ≥ 7 days post-CT; persistent AML in blood or bone marrow
Aplasia	Patient survives ≥ 7 days post-CT; death while cytopenic, with aplastic bone marrow
Indeterminate cause	Patients who die < 7 days posttherapy Patients who die > 7 days posttherapy with no PB blasts, but no bone marrow examination Patients who do not complete the first course of therapy
Morphologic relapse	Reappearance of blasts post-CR in PB or bone marrow
Molecular or cytogenetic relapse	Reappearance of molecular or cytogenetic abnormality

Abbreviations: AML, acute myelogenous leukemia; CT, chemotherapy; PB, peripheral blood; CR, complete remission.

APPENDIX F
NCI Common Toxicity Criteria Version 4.03 (CTCAE)
Active Date: June 14, 2010

Toxicity will be scored using NCI CTC Version 4.03 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.03 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version 4.03.

APPENDIX G. Assessment of other geriatric syndromes

1. Have you had any falls in the last 6 months?

   Yes No

   Comments regarding falls(ie: specify number of falls)_____

2. Have you had a period of confusion (delirium) in the past?

   Yes No

   Comments regarding dementia or delirium: _____

3. Do you have a history of urine leakage (incontinence)?

   Yes No

4. Do you have a history of stool leakage (incontinence)?

   Yes No

   Comments regarding urinary or stool incontinence: _____