Research Proposal

(Version No.: 2 .0 Date: 2026.05 .08)

Project Name: VA-CAG Two-Week Regimen vs. Three-Week Regimen for Induction Remission in Newly Diagnosed Acute Myeloid Leukemia — A Prospective, Multicenter, Randomized Controlled Trial

Sponsor: The 920th Hospital of the Logistics Support Force

Department in Charge: Department of Hematology

Principal Investigator: Wang Sanbin

Participating Institutions: The First Affiliated Hospital of Kunming Medical University, Yunnan University Affiliated Hospital, Qujing First People’s Hospital, Pu’er People’s Hospital, Dali University Affiliated Hospital, etc.

Investigator’ s Declaration and Protocol Signature Page

As the principal investigator of this research project, I will adhere to the Ministry of Health’ s “Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects ” (2023), the “ Administrative Measures for Investigator-Initiated Clinical Research Conducted by Healthcare Institutions” (2024),the "Declaration of Helsinki" (2024), the CIOMS "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (2002), and the ethical principles of GCP. Under the guidance of the Good Clinical Practice (GCP) guidelines, I will use the protocol approved by the Ethics Committee and conduct the study in accordance with the requirements of this protocol to ensure the scientific integrity of the research and protect the health and rights of the study participants.

Name: Wang Sanbin

Signature (Handwritten): _____

Date: _____

Protocol Summary

Protocol Title	VA-CAG Two-Week Regimen vs. Three-Week Regimen for Induction Remission in Newly Diagnosed Acute Myeloid Leukemia——A Prospective, Multicenter, Randomized Controlled Trial
Version No./Date	3.0/March 19, 2026
Participating Institutions	The First Affiliated Hospital of Kunming Medical University Yunnan University Affiliated Hospital Pu'er People's Hospital Qujing First People’s Hospital Dali University Affiliated Hospital Baoshan People's Hospital Northeastern Yunnan Regional Central Hospital Lijiang People's Hospital
Principal Investigator	Wang Sanbin
Study Design	IIT Randomized Controlled Trial
Study Objective	To compare the efficacy and safety of the two-week versus three-week VA-CAG regimens in inducing remission in patients with newly diagnosed acute myeloid leukemia

Sample Size	A total of 110 patients were randomly assigned in a 1:1 ratio to the experimental group and the control group.
Study Population	Adult patients with acute myeloid leukemia
Study Design	Prospective, multicenter, randomized controlled, open-label
Inclusion Criteria	1) Diagnosis of acute myeloid leukemia confirmed according to NCCN guidelines; 2) Age 18－75 years; 3) Body weight 30－100 kg; 4) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3; 5) No significant organ dysfunction (echocardiographic ejection fraction >45%; bilirubin <2 times the upper limit of normal; AST and ALT <3 times the upper limit of normal; serum creatinine <2 times the upper limit of normal); 6) No severe infections; 7) Study participants voluntarily agree to participate in this clinical trial and sign an informed consent form.
Exclusion Criteria	1) Patients with other types of diseases; 2) Patients with a projected survival of less than 1 month; 3) History of prior treatment; 4) Severe psychiatric or neurological disorders that impair the ability to provide informed consent and/or report or observe adverse events; 5) Other circumstances deemed unsuitable for enrollment by the investigator.
Endpoints	The last enrolled patient reaches the study endpoint
Withdrawal/Exclusion Criteria	Participants who experience changes in their condition unrelated to the study factors during treatment or follow-up and cannot continue to be observed.
Early withdrawal criteria	1. Patients who experience severe, intolerable adverse reactions; 2. Treatment failure or lack of response; 3. The participant voluntarily requests withdrawal, or the investigator determines that

	the participant is unsuitable for continued treatment for other reasons; 4. Participants for whom continued use of the investigational drug is not appropriate or who cannot continue to follow the study protocol.
Dosage Regimen	Specific Medication for the VACAG Protocol: (1) Two-week regimen group Azacitidine: 75 mg/m² on days 1 – 7 by subcutaneous injection, Venetoclax: 100 mg on Day 1, 200 mg on Day 2, 400 mg on Days 3 – 14, oral, Arubicin: 12 – 14 mg/m² on days 1, 3, 5, and 7 (IV infusion), Cytarabine: 10 mg/m² every 12 hours on days 1 – 7, subcutaneous injection, Recombinant human granulocyte colony-stimulating factor: 5 μg/kg on days 0 – 8; discontinue if WBC > 20 × 10⁹/L; (2) Three-week regimen group Venetoclax administered for 21 days; dosage and administration are the same as in the 2-week regimen group.
Primary Efficacy Endpoint	Complete remission (CR) rates in both groups as assessed by post-chemotherapy bone marrow cytology
Secondary Efficacy Endpoints	1. Flow cytometry-detected minimal residual disease (MRD) remission rate 2. Duration of myelosuppression 3. Incidence of adverse events 4. 2-year overall survival (2y-OS) 5. 2-year event-free survival (2y-EFS)
Safety Endpoints	1. Adverse events 2. Chemotherapy-related mortality Risk of fungal breakthrough infection
Study Progress Plan	2-year patient enrollment, 1-year follow-up
Statistical Analysis	t-test, chi-square test, Kaplan-Meier method

Methods	
Publication Format	SCI-indexed papers, Chinese core journals

一、 Research Objectives

1. Primary Objective

To compare the efficacy and safety of the two-week and three-week VA-CAG regimens in inducing remission in acute myeloid leukemia.

2. Secondary Objectives

(1). To compare the composite complete remission rate and event-free survival rate between the two groups.

(2). To compare the minimal residual disease (MRD)-negative rates between the two groups.

(3). To evaluate safety and tolerability in both groups, with particular focus on adverse events related to myelosuppression.

二、 Study Background

I. Current Status of Acute Myeloid Leukemia Treatment

Acute myeloid leukemia (AML) is one of the most common hematologic malignancies, with an annual incidence of approximately 4 per 100,000 people. The incidence increases with age, and **the median age at diagnosis is 68 years** [1].The overall prognosis for AML patients is poor, with a 5-year survival rate of only 27.8% [1], and the

prognosis worsens with increasing age. Among adult patients under 60 years of age, 35% – 40% can achieve long-term remission, whereas only 5% – 15% of patients over 60 years of age achieve long-term remission [2].

Treatment for AML must be individualized based on the patient's disease risk, age, and performance status.Currently, the standard induction chemotherapy regimen for newly diagnosed AML typically consists of anthracycline-based chemotherapy combined with cytarabine, achieving an overall response rate **(ORR) of approximately** 70%. Building on this foundation, clinical centers may also add agents such as homoharringtonine or mitoxantrone at their discretion to further improve response rates based on the patient's specific condition.**Elder**ly patients constitute a significant proportion of the AML population. Due to **advanced age and multiple comorbidities, they often cannot tolerate intensive chemotherapy**. Clinically, pre-induction regimens or regimens containing low-dose cytarabine may be adopted to ensure treatment safety; however, **the complete remission rate** with traditional treatment regimens **is only 43%** [3 – 5]. When induction therapy fails, particularly in patients with multiple relapses, subsequent treatment options are extremely limited.

With the continuous advancement of stratified diagnosis and treatment and the introduction of new drugs, AML therapy is gradually

entering the era of targeted therapy. Although many patients with newly diagnosed and relapsed AML have benefited from this, for those with frequent relapses, poor general condition, and a strong desire for treatment, **achieving remission again and proceeding to transplantation is of critical importance**.Because patients with relapsed/refractory AML have previously undergone multiple courses of chemotherapy, current treatments are characterized by significant individual variability, high mortality risk, and widespread drug resistance. Even if remission is achieved with intensive chemotherapy, the risk of chemotherapy-related deaths from infections and bleeding increases accordingly, failing to provide patients with true benefit. Therefore, the search for safe and effective AML treatment regimens is an urgent priority.

II. Advances in Acute Myeloid Leukemia Treatment with Venetoclax-Containing Regimens

In recent years, various new drugs and treatment regimens have gradually been introduced into clinical practice. Targeted therapies, led by venetoclax (VEN), have ushered in a new era in AML treatment.BCL-2 is a member of the anti-apoptotic protein subfamily that inhibits cell apoptosis. Overexpression of BCL-2 is observed in various hematologic malignancies, making BCL-2 targeting a promising therapeutic approach for these diseases. It has been

confirmed that BCL-2 is overexpressed in AML cells, where it mediates tumor cell survival and is associated with resistance to chemotherapy drugs.Venetoclax works by directly binding to the BCL-2 protein, displacing and releasing pro-apoptotic proteins such as BIM and BAX. The released pro-apoptotic proteins interact with each other, triggering an apoptotic cascade that leads to the death of malignant cells [6]. This mechanism of action, which targets the BCL-2 protein, is innovative and unique in the treatment of AML.

The global Phase III VIALE-A clinical trial demonstrated that venetoclax combined with hypomethylating agents (HMAs) in the treatment of elderly patients with newly diagnosed AML achieved **a complete remission (CR) rate of 67%, an overall response rate (ORR) of** 73%, and a median overall survival (OS) of 16.6 months [7].

In addition to combination with hypomethylating agents, venetoclax is currently being **used in combination with other conventional chemotherapies** for induction therapy in AML and has demonstrated promising efficacy.A team led by Professor Zhu Honghu at the First Affiliated Hospital of Zhejiang University enrolled 33 patients with newly diagnosed AML and treated them with venetoclax in combination with the traditional intensive chemotherapy regimen DA (daunorubicin and cytarabine), achieving a CR rate of 91% (30/33) and an MRD remission rate of 97% (29/30) [11].An international study

using FLAG-IDA (fludarabine, cytarabine, demethoxydaunorubicin) in combination with venetoclax to treat newly diagnosed AML reported bone marrow remission and MRD remission rates of 70% and 96%, respectively.[12] Another study reported that the use of venetoclax in combination with the CLIA regimen (cladribine, idarubicin, and cytarabine) for the treatment of newly diagnosed AML achieved a CR rate of 84% and an MRD remission rate of 82% [13]. The above regimens combining venetoclax with intensive chemotherapy can achieve high remission rates; however, the duration of bone marrow suppression generally exceeds 2 weeks, leading to high rates of infection and bleeding, as well as significant adverse reactions.

III. Exploration of VACAG Induction Regimens and Full-Course Treatment with Venetoclax-Containing Regimens for Acute Myeloid Leukemia

Our center previously conducted a study using venetoclax plus azacitidine combined with modified CAG (VACAG regimen) to treat 114 patients with newly diagnosed AML. The median age was 50 years. After one treatment cycle, the CR rate and composite CR rate were 90% (95% CI 85 – 96%) and 95% (95% CI 91 – 99%), respectively.The minimal residual disease (MRD) remission rate was 83%. No serious adverse events occurred. The median duration of Grade 4 neutropenia and Grade 4 thrombocytopenia was 14 days (IQR,

9 – 19) and 10 days (IQR, 4 – 16), respectively, and the 60-day mortality rate was 0%.After a median follow-up of 13.3 months, the 1-year OS and 1-year RFS were 86% (95% CI 78 – 92%) and 75% (95% CI 65 – 83%), respectively.

Previously, our VA-CAG regimen achieved good efficacy, but it was applicable only to fit patients aged 18 – 65 years; clinical data on its applicability to elderly and frail patients are still lacking.Currently, numerous clinical studies are exploring the optimal dose of venetoclax for the treatment of AML through dose reduction. A study from the Mayo Clinic enrolled 270 patients with newly diagnosed AML; during the first cycle, these patients received venetoclax regimens of 14 days (n=40, 15%), 21 days (n=41, 15%), and 28 days (n=189, 70%).Patients treated with venetoclax for 14 days (68%), 21 days (66%), and 28 days (62%) had similar CR/CRi rates and survival rates, with median survival times of 18.6 months, 21.3 months, and 13.2 months, respectively.Furthermore, relevant findings from retrospective studies of different venetoclax dosing regimens were reviewed; with the exception of one study, all studies demonstrated that shorter-duration venetoclax regimens were non-inferior in terms of complete/partial remission rates and showed a trend toward reduced infection rates [14].In summary, short-course venetoclasib in AML may be as effective as standard-course regimens while causing less bone marrow

toxicity. Furthermore, shortening the venetoclasib course (or adopting intermittent dosing) may help prevent the development of drug resistance, as continuous administration may exert selective pressure on cells, leading them to develop resistance mechanisms.Furthermore, a real-world study of Chinese AML patients showed that the median age of patients receiving venetoclax combined with azacitidine was 71.5 years (range 65–82 years), and all patients were deemed unsuitable for intensive therapy due to advanced age or comorbidities. In this study, the half-dose VEN-AZA regimen (200 mg/day) demonstrated unprecedented efficacy (100% CR/CRi, median survival >24.6 months) and good safety in Chinese AML patients unsuitable for intensive chemotherapy. In contrast, the three-week VA-CAG regimen previously implemented at our center for the treatment of newly diagnosed AML patients aged 18–65 years is currently being modified to reduce the duration of venetoclax administration to two weeks to minimize drug-related adverse reactions and the duration of myelosuppression; based on this adjustment, the upper age limit for enrolled patients may be increased to 75 years. [20]

Based on the above clinical evidence, our center plans to shorten the venetoclax treatment duration from 3 weeks to 2 weeks to explore the

optimal duration of venetoclax use in the VA-CAG regimen. Concurrently, we will extend the upper age limit for enrolled patients to compare the safety and efficacy of the 3-week and 2-week regimens across different age groups.

三、 Trial Rationale

1. Preliminary animal studies and literature review

BCL-2 is a member of the anti-apoptotic protein subfamily and functions to inhibit apoptosis. BCL-2 is overexpressed in various hematologic malignancies, and targeting BCL-2 holds broad application potential in the treatment of these cancers. It has been demonstrated that BCL-2 is overexpressed in AML cells, where it mediates tumor cell survival and is associated with resistance to chemotherapy drugs.Venetoclax works by directly binding to the BCL-2 protein, displacing and releasing pro-apoptotic proteins such as BIM and BAX. The released pro-apoptotic proteins interact with each other, initiating an apoptotic cascade that leads to the apoptosis of malignant cells [15–17]. This mechanism of action, which targets the BCL-2 protein, is innovative and unique in the treatment of AML.

The Oral35 study, presented at the 2021 ASH meeting,

enrolled 27 untreated patients aged 18–59 years with ELN-defined high-risk AML. After 1–2 cycles of treatment with the regimen of decitabine (20 mg/m^2,d1–5) in combination with venetoclax (100 mg–200 mg–400 mg, 28 days) for 1–2 cycles. Compared with a historical cohort receiving intensive chemotherapy, the composite remission rate was 95.7% vs. 73.6% (p = 0.044),and the MRD response rate was 73.9% vs. 43.4% (p=0.023), both significantly superior to the historical cohort. Additionally, the incidence of infections during treatment was lower, red blood cell and platelet transfusions were reduced, and the 30-day and 60-day mortality rates were 0% [18].Similarly, the Abstract 2334 study presented at the 2021 ASH meeting enrolled 33 patients with newly diagnosed AML, with a median age of 40 years. After one cycle of treatment with venetoclax combined with a conventional intensive DA regimen, the CR rate reached 91% (30/33). With a median follow-up of 118.5 days, no patients relapsed or died, and the median EFS and OS had not yet been reached [19].The vinclastine-based combination regimens described above have demonstrated good efficacy, deep remissions, and improved safety in

both ELN-high-risk AML patients and young patients with newly diagnosed AML.

Our department presented the results of a prospective, multicenter, Phase II clinical trial evaluating the efficacy of venetoclax combined with azacitidine, cytarabine, aclamycin, and granulocyte colony-stimulating factor (VA-CAG regimen) in patients with newly diagnosed acute myeloid leukemia at the 29th Annual Meeting of the European Hematology Association (EHA) in 2024:As of January 25, 2024, a total of 67 patients had been enrolled, treated, and completed the initial efficacy assessment.The median age of all patients was 51 years; 44.8% were in the high-risk group, 28.4% in the intermediate-risk group, and 5.9% in the low-risk group. Regarding efficacy, 98.5% of patients achieved remission after one cycle of chemotherapy, including 94.0% in complete remission and 4.5% in partial remission.82.5% of patients achieved negative minimal residual disease. The incidence rates of Grade 4 neutropenia, thrombocytopenia, and infection were 97.0%, 85.1%, and 14.9%, respectively. The duration of neutropenia and severe thrombocytopenia was 13.5 days and

7 days, respectively. The median red blood cell and platelet transfusion volumes were 6 units and 30 units, respectively. Fungal breakthrough infections occurred in 10.4% of patients, and bacteremia occurred in 4.5% of patients; all were controlled following antimicrobial therapy. No treatment-related deaths occurred. After a median follow-up of 6 months, 14 patients underwent hematopoietic stem cell transplantation, with an overall survival rate of 92.5%.

2. Criteria for Study Participant Selection

Our center previously implemented a 3-week VA-CAG regimen for the treatment of newly diagnosed AML in patients aged 18–65 years. We now propose reducing the duration of venetoclax administration to 2 weeks to minimize drug-related adverse reactions and the duration of bone marrow suppression. Based on this adjustment, the upper age limit for enrollment can be extended to 75 years.

四、 Study Content

1. Study Population/Data

Patients aged 18–75 years with newly diagnosed acute myeloid leukemia, as defined by the 2026 V2.0 NCCN Guidelines.

2. Sample Size Calculation or Subgroup Data

Based on data from previous pivotal studies and clinical practice, the complete remission (CR) rate in the control group (21-day venetoclax regimen) is assumed to be 90%. To test for non-inferiority, the experimental group (14-day regimen) is hypothesized to have the same CR rate (90%). Non-inferiority margin: set at Δ = 10%. Dropout rate: estimated at 10%.Based on the above parameters, calculations were performed using the "Two-Proportion Non-Inferiority Test" module in PASS 2021 software (or the SAS PROC POWER procedure). Under the conditions of α = 0.05 (one-sided), power = 80%, Pc = Pe = 0.90, and non-inferiority margin Δ = 0.10, the calculation determined that 110 evaluable patients are required in each group.

Final Enrollment Target: Therefore, this study plans to recruit a total of 110 patients, who will be randomly assigned in a 1:1 ratio to the experimental group and the control group. This sample size will provide sufficient statistical power to test the primary hypothesis that "the 14-day regimen is non-inferior to the 21-day regimen in terms of CR rate (non-inferiority margin of 10%)."

3. Specific Study Content (Primary Endpoints)

This study will enroll patients with newly diagnosed acute myeloid leukemia (AML) and employ a prospective, multicenter, open-label, randomized controlled trial to compare the remission rates and safety of the VA-CAG 2-week regimen versus the 3-week regimen in inducing remission in AML patients.

The primary endpoint is the complete remission rate; secondary endpoints include flow cytometric minimal residual disease (MRD) remission rate, duration of bone marrow suppression, incidence of adverse events, 2-year overall survival (2y-OS), and 2-year event-free survival (2-EFS).

五、 Study Methods

1. Inclusion Criteria (Diagnostic Criteria, Eligibility Criteria, Exclusion Criteria)

Inclusion Criteria: 1. Acute myeloid leukemia (AML) diagnosed according to NCCN guidelines; 2. Age 18–75 years; 3. Body weight 30–100 kg; 4. ECOG performance status ≤ 3;5. No significant organ dysfunction (ECG ejection fraction >45%; bilirubin <2 times the upper limit of normal; AST and ALT <3 times the upper limit of normal;

serum creatinine <2 times the upper limit of normal); 6. No severe infection; 7. Study participants voluntarily agree to participate in this clinical trial and sign an informed consent form.

Exclusion Criteria: 1. Patients with other types of diseases; 2. Expected survival of less than 1 month; 3. History of prior treatment; 4. Severe psychiatric or neurological disorders that affect the ability to provide informed consent and/or report or observe adverse events; 5. Other conditions deemed unsuitable for enrollment by the investigator.

2. Participant Grouping

This study employs a stratified block randomization method to assign participants in a 1:1 ratio to either the two-week regimen group (VACAG, vinorelbine administered for 14 days per cycle) or the three-week regimen group (VACAG, vinorelbine administered for 21 days per cycle).Randomization will be based on the following stratification factors: Stratificationage: by 18－40 years vs. 41－65 years vs. 66－75 years. Arandomization method block withblock sizes variable will be used to ensure balance in. the number of participants between

the two groupsThe procedure specific randomization is as follows:

a) Upon enrollment, patients are first assigned to a stratum (e.g., a 55-year-old patient → 41–65 years → Stratum 2)

b) Randomization is conducted independently within each stratum (block randomization may be used, with block size typically set to 4)

c) The treatment groups are allocated in equal proportions within each stratum (e.g., 1:1)

3. Experimental treatment (if any)

1) Dosage Selection/Adjustment

Specific medications for the VACAG regimen:

Azacitidine: 75 mg/m² on days 1–7 by subcutaneous injection,

Venetoclax: 100 mg on Day 1, 200 mg on Day 2, 400 mg on Days 3–14, oral,

Arubicin: 12–14 mg/m² on days 1, 3, 5, and 7 (IV infusion),

Cytarabine: 10 mg/m² every 12 hours on days 1–7 (subcutaneous injection),

Recombinant human granulocyte colony-stimulating

factor: 5 μg/kg on days 0–8; discontinue if WBC > 20 × 10^9/L;

2) Trial Blinding/Unblinding

Open-label design: Due to the differing treatment durations between the two groups (14 days vs. 21 days), implementing a "double-blind" protocol for both patients and physicians would be extremely difficult and costly. Therefore, this study employs an open-label design.

3) Criteria for Concomitant Medications

4) Rescue Medications and Supportive Care (necessary therapeutic measures in the event of study-related SAEs)

To ensure patient safety, all study participants must receive standardized infection prevention measures, appropriate blood product support, and TLS prevention.

- Infection prevention: Closely monitor infection indicators; if infection occurs, actively seek evidence of the pathogen and provide effective antimicrobial therapy.
- Hematologic support: The threshold for platelet

transfusion is $\leq 10 \times 10^9$/L ($\leq 20 \times 10^9$/L if at risk); the threshold for red blood cell transfusion is Hb ≤ 60 g/L. The use of G-CSF is permitted and recommended.

· TLS Prevention: All patients must undergo hydration and uric acid-lowering therapy prior to treatment.

· Each study site must adhere to this protocol and document all supportive care medications and transfusions.

If a study participant experiences intolerable adverse effects during treatment that the investigator determines are caused by veneclar, veneclar should be discontinued, while other medications should continue as planned.

4. Criteria for early withdrawal or termination of the trial

(1) Patients with intolerable serious adverse reactions:

① An intolerable Grade 4 or higher non-hematologic adverse event related to the study drug that does not resolve or recurs despite active supportive treatment, resulting in prolonged treatment interruption. For example:

a) Hepatotoxicity: Drug-induced liver injury reaching Grade 4 (ALT/AST > 20 times the upper limit of normal, accompanied by symptoms or elevated bilirubin, or liver dysfunction).

b) Gastrointestinal toxicity: Grade 4 diarrhea, nausea/vomiting, or mucositis that does not respond to standard treatment.

c) Infection: Severe or opportunistic infection of Grade 4 or higher (requiring hospitalization and intravenous treatment).

d) Other: Uncontrollable Grade 4 or higher non-hematologic toxicity, such as neurotoxicity, cardiotoxicity, pancreatitis, etc.

e) Specific and severe drug-related reactions: For example, veneclarib-related tumor lysis syndrome (Grade 4, even after prophylaxis), or any life-threatening hypersensitivity reaction.

② Persistent and difficult-to-correct Grade 4 hematologic toxicity (e.g., neutropenia or thrombocytopenia) resulting in prolonged inability to use the study drug (e.g., continuous interruption exceeding 42 days), and where the investigator determines that the

risks of continuing the study outweigh the benefits.

(2) Treatment failure or ineffectiveness:

a) Disease progression: AML disease progression confirmed by bone marrow or peripheral blood assessment.

b) Treatment failure: Failure to achieve any morphological remission (e.g., persistent leukemic status) after completion of at least 2 treatment cycles, and the investigator determines that continued treatment offers no clinical benefit.

(3) The study participant voluntarily withdraws, or the investigator determines that the participant is unsuitable for continued treatment for other reasons; those for whom continued use of the investigational drug is not appropriate or who cannot continue the study protocol;

Participants for whom continued use of the investigational drug is not appropriate or who cannot continue with the study protocol.

六、 Trial Procedures

1. Participant Management/Data Collection

1) Recruitment Method and Data Collection Timeframe

The study will be conducted specifically for patients

with newly diagnosed AML at the Hematology Department of the 920th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army, as well as in the outpatient and inpatient departments of participating institutions' hematology departments. Participants will be thoroughly screened and recruited. Additionally, word-of-mouth among patients may be used to inform potential participants and encourage them to visit the hospital for screening and enrollment.

2) Informed Consent Process

① In the participant reception room or consultation room, the entire content of the informed consent form will be explained in detail to the participant using language they can understand, avoiding technical jargon, and without inducing or influencing the participant to join or continue participating in the trial;

② Fully respect the research participant's right to informed consent and their right to withdraw from the trial at any time;

③ Provide the research participant and their legal representative with sufficient time and opportunity to

ask questions about the trial details and to make an independent decision regarding participation;

④ The informed consent form must be signed and dated by the research participant personally;

⑤ If a research participant is unable to read or sign the informed consent form, the form may be signed and dated by a legal representative after full disclosure. The legal representative must indicate their relationship to the research participant. For hospitalized patients, if the informed consent form is signed by a legal representative, the signature must match the signature on file in the medical record;

⑥ If changes are made to the informed consent form during the trial, the Ethics Committee's approval must be obtained, and the research participant currently enrolled in the trial must provide informed consent again. The trial may only continue after the research participant's consent is obtained and the informed consent form is signed;

⑦ The investigator conducting the informed consent process must sign and date the informed consent form;

⑧ The dates of signature by the research participant

and the investigator must match;

⑨ One copy of the signed and dated written informed consent form shall be provided to the research participant or their legal representative for safekeeping, and one copy shall be retained by the investigator.

3) Verify inclusion and exclusion criteria

4) Review medical history and medication history

5) Assignment of Screening Numbers

To ensure the uniqueness and independence of participant identification across all study sites, the following screening number system is adopted:

· Numbering format: Center code-S-sequence number. (Center code: A two-digit code pre-assigned to each participating center, e.g., 01, 02, … Sequence number: A three-digit number starting from "001" at each center, incremented sequentially based on the order in which study participants sign the informed consent form.)

· Assignment and Management: Upon signing the informed consent form, each study participant is assigned a unique screening code. Each research center

must maintain a "Screening and Enrollment Form" to record all study participants' screening codes, initials, date of informed consent, and screening results. This screening code is used solely for management during the screening period and is not used for randomization or final identification.

Eligible research participants will be formally enrolled. Using a stratified cluster randomization method, participants will be assigned in a 1:1 ratio to either the two-week regimen group (VACAG, vinorelbine administered for 14 days per cycle) or the three-week regimen group (VACAG, vinorelbine administered for 21 days per cycle).

6) Data Analysis or Analysis of Study Results

Each site collects data and submits it periodically to the central site. Data analysis is conducted by the principal investigator or research assistant at the central site under the guidance of a statistician. Interim workshops are held periodically to present the results of preliminary data analysis.

2. Safety Evaluation Procedures (Assessment, Detection, and Reporting of Adverse Events)

Safety will be monitored by identifying and evaluating potential adverse reactions associated with the treatment in each treatment cycle. Patients will be assessed for potential treatment-related toxicity through medical history, physical examination, blood tests, and other examinations. All adverse events occurring during the study must be recorded.All adverse events must be monitored until they are resolved, stabilized, or until it is confirmed that the study treatment or participation was not the cause. Serious adverse events that persist at the end of the study must be monitored until a final outcome is determined. Any serious adverse events occurring after the study that are considered potentially related to the study treatment or participation must be recorded and reported promptly.

3. Discontinuation/Withdrawal Procedures

The study will be terminated under the following circumstances: 1. If a study participant experiences a Grade 3 or higher adverse event following administration of the investigational drug, and this event is identified as arising from the treatment

regimen of this clinical trial, the protocol will be modified to reduce the dose of the investigational drug based on the nature of the adverse event. 2. If the investigator or any independent review committee or regulatory authority determines that the trial poses a safety risk to study participants, the clinical trial will be terminated.3. If the investigator decides to terminate the clinical trial, the trial will be terminated.

七、 Start and End of the Trial

Start of the Study: The study begins when the first participant signs the informed consent form and is enrolled;

Study End: The last enrolled patient reaches the observation endpoint (2-year overall survival [2y-OS], 2-year event-free survival [2y-EFS]) and completes the 24-month efficacy and safety follow-up after treatment.

八、 Data Safety and Monitoring Plan (including research team members and authorization of responsibilities)

1. Data Management Methods and Authorization Responsibilities

①List of Technical Staff and Division of Responsibilities in the Department of Hematology, 920th Hospital of the Joint Logistics Support Force

	Name		Title	Responsibilities	Signature

No.		Department			of Confirmation
1	Wang Sanbin	920 Hospital	Principal Investigator	Assignment of Research Tasks	
2	Li Xiaoping	920 Hospital	Study Physician	Research participant screening (e.g., determination of inclusion and exclusion criteria, physical examination)	
3	Liu Lin	920 Hospital	Research Physician	Informed consent-related tasks (e.g., explaining the ICF, witnessing the signing)	
4	Chen Yingnian	920 Hospital	Research Nurse	Trial procedures (e.g., medication administration, blood collection, sample handling)	
5	Yang Xin	920 Hospital	Research Assistant	Data management (e.g., CRF completion, EDC data entry, SDV support)	
6	Ma Yongguo	920 Hospital	Principal Investigator	Safety Management (e.g., AE/SAE documentation, reporting coordination)	

②List of Roles at the Research Center

No.	Department	Role
1	Department of Hematology, 920th Hospital of the Joint Logistics Support Force (Initiating Unit)	Project coordination, patient enrollment assessment, clinical diagnosis and treatment, efficacy evaluation, statistical analysis, and report writing.
2	The First Affiliated Hospital of Kunming Medical University (Participating	Patient evaluation, clinical diagnosis and treatment, efficacy assessment

	Institution)	
3	Yunnan University Affiliated Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation
4	Pu'er People's Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation
5	Qujing First People’s Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation
6	Dali University Affiliated Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation
7	Baoshan People’s Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation
8	Northeastern Yunnan Regional Central Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation
9	Lijiang People’s Hospital (Participating Institution)	Patient assessment, clinical diagnosis and treatment, efficacy evaluation

九、 Compliance with Ethical Principles and Relevant Regulations

This study complies with the "Good Clinical Practice (GCP) for Drug Clinical Trials," the "Administrative Measures for Investigator-Initiated Clinical Research Conducted by Healthcare Institutions (Trial Version)," and the Declaration of Helsinki. This study may only proceed after the protocol has been approved by our hospital’s Ethics

Committee prior to the trial’s commencement. If protocol amendments are necessary during the study, the revised protocol must be resubmitted to the Ethics Committee for review, and the investigator must await the Ethics Committee’s approval before implementing the new protocol.

Each enrolled patient must sign an informed consent form. A copy of the informed consent form, along with the contact information for the investigator and the Ethics Committee, must be provided to the study participants. This study will collect clinical data and personal information from study subjects for scientific research purposes, which may involve the protection of patients’ privacy rights.All study participants and data analysts have signed confidentiality agreements and will not disclose patients’ personal information or disease-related information to any individuals or institutions unrelated to this study. Collected patient data will be managed uniformly to prevent any leakage of personal privacy.

十、 Statistical Analysis Plan

This study will conduct an efficacy analysis on all randomized patients. The primary endpoint, the complete response (CR) rate, will be evaluated using a logistic

regression model (which includes age-stratified covariates). The non-inferiority of the 14-day regimen compared to the 21-day regimen will be determined by testing whether the upper limit of the 95% confidence interval for the hazard ratio is less than the pre-specified non-inferiority margin of 1.25. Secondary endpoints include 2-year overall survival (OS) and 2-year event-free survival (EFS), which will be analyzed using the chi-square test/Fisher's exact test and descriptive statistics, respectively. Tests will be one-sided, with a significance level set at $\alpha = 0.05$. Additionally, in the pre-specified subgroup analyses, efficacy estimates and their 95% confidence intervals will be reported separately for the two age subgroups: 18–65 years and 65–75 years.

十一、 Publication of Research Findings

We plan to publish two SCI-indexed papers and two articles in Chinese core journals.

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