Official Title: A PHASE 1, OPEN-LABEL, SAFETY, TOLERABILITY, AND EFFICACY STUDY OF NC525 IN SUBJECTS WITH ADVANCED MYELOID NEOPLASMS

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A PHASE 1, OPEN-LABEL, SAFETY, TOLERABILITY, AND EFFICACY STUDY OF NC525 IN SUBJECTS WITH ADVANCED MYELOID NEOPLASMS

Sponsor Protocol Number: NC525-01

IND Number: 157274

Investigation Product: NC525 [LAIR-1 IgG1 Humanized Monoclonal Antibody]

Phase of Study: 1

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PROTOCOL SYNOPSIS

HYPOTHESIS

Treatment with NC525, a humanized immunoglobulin gamma 1, kappa (IgG1κ) monoclonal antibody specific for LAIR-1, will, specifically kill leukemic cells while sparing healthy cells in both the bone-marrow and the periphery, ameliorating disease with minimal toxicity, and resulting in clinical benefit for subjects with advanced myeloid neoplasms.

STUDY OBJECTIVES

Primary Objectives

1) To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of NC525
2) The recommended Phase 2 dose (RP2D) of NC525 will be defined in subjects with advanced myeloid neoplasms
3) Define a minimally active dose (MAD), pharmacologically active dose (PAD), and maximum tolerated dose (MTD) of NC525 in subjects with advanced myeloid neoplasms

Secondary Objectives

1) To evaluate the clinical benefit of NC525
2) To evaluate the time to achieve an objective response (OR)
3) To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of NC525

Exploratory Objectives

1) To assess the immunogenicity of NC525
2) To explore biomarkers that may predict the pharmacologic activity of NC525

STUDY ENDPOINTS

Primary Endpoints

1) Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs). **Note:** Toxicity grading per NCI CTCAE v5.0
2) The recommended Phase 2 dose (RP2D) of NC525 in subjects with advanced myeloid neoplasms.
3) The MAD, PAD, and MTD of NC525 will be defined in subjects with advanced myeloid neoplasms.

Secondary Endpoints

1) Assessment of anti-leukemia activity/efficacy will be used to evaluate the clinical benefit of NC525, including:
    a. Objective Response (OR)
        i. CR, CRi, or CRh and MLFS
    b. Event-free survival (EFS), and

c. Overall survival (OS)

2) Assessment of time to achieve response, defined as CR, CRi, or CRh

   a. To evaluate the time to achieve an objective response from Cycle 1 Day 1 to day remission is achieved as defined per protocol

3) Assessment of PK of NC525 concentration(s) in serum, as well as assessment of the PK/PD profile

Exploratory Endpoints

1) Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC525 will be determined

2) Biomarker effects of NC525 in peripheral blood and bone marrow will be assessed, including but not limited to the following:

   a. Percentage and/or expression level of LAIR-1 blast cells and/or Leukemic Stem Cells (LSC) or Hematopoietic Stem Cells (HSC)

   b. Any relation to response (clearing of blast cells to achieving CR)

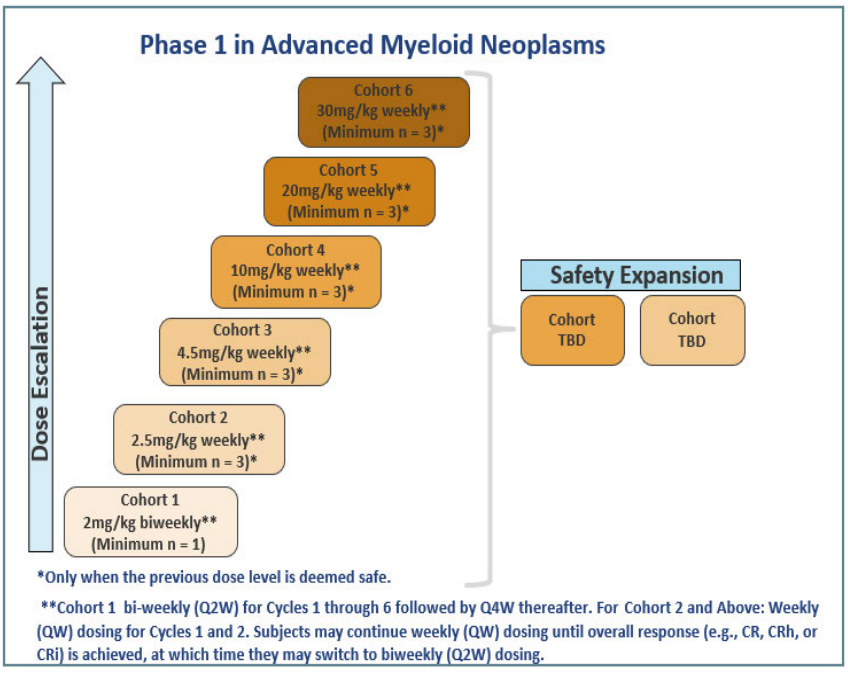
   c. Serum markers of inflammation or immune modulation (cytokine & chemokine levels)

STUDY DESIGN

Description

This is an open-label, non-randomized, Phase 1 study to determine the safety and tolerability of NC525. This study will also assess the clinical benefit in subjects with advanced myeloid neoplasms. The study includes a dose escalation phase to determine MTD followed by expansion cohorts to further evaluate the safety and tolerability of the MTD (Figure S1).

Figure S1: Phase 1 Study Design



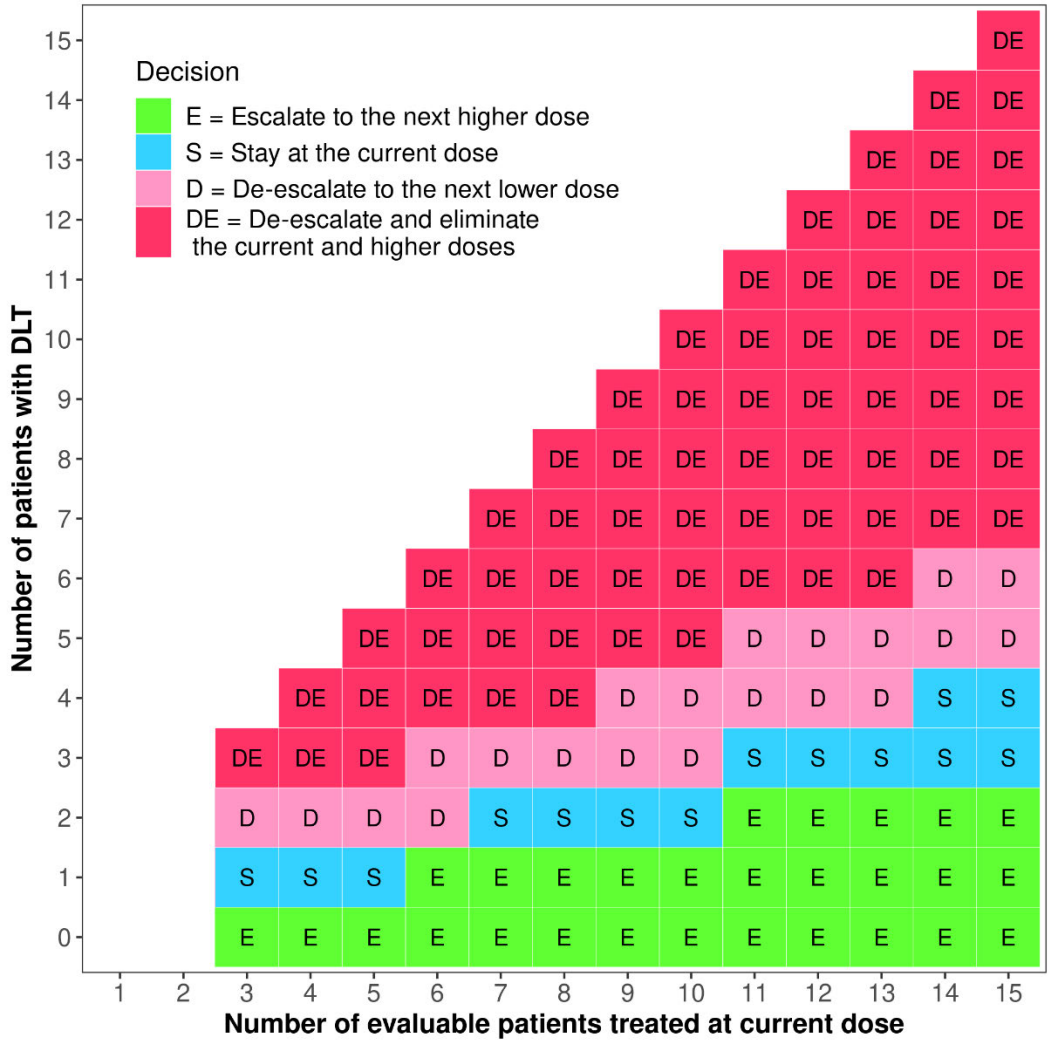
The safety and tolerability of NC525 will be evaluated by escalating dose levels of NC525. In addition, the minimally active dose (MAD), pharmacologically active dose (PAD), and maximum tolerated dose (MTD), of NC525 will be determined.

The PAD will be defined as a dose that provides a maximal biologic effect, such as achieving a complete remission (CR) and other variants of complete remission (CRh, CRi), and/or the MTD of NC525.

Once the biologically-effective dose(s) deemed to be safe have been identified, safety and tolerability will be further assessed through expansion of two dose levels to determine an optimal biologically active Recommended Phase 2 Dose (RP2D) and administration schedule of NC525.

A Bayesian Optimal Interval (BOIN) design (Figure S2) for Phase I clinical trials (Liu 2015) with a target dose-limiting toxicity (DLT) rate of approximately 25% will be applied for dose escalation and confirmation to determine a recommended Phase 2 dose (RP2D) for NC525.

Figure S2: Dose-Finding Rules per BOIN



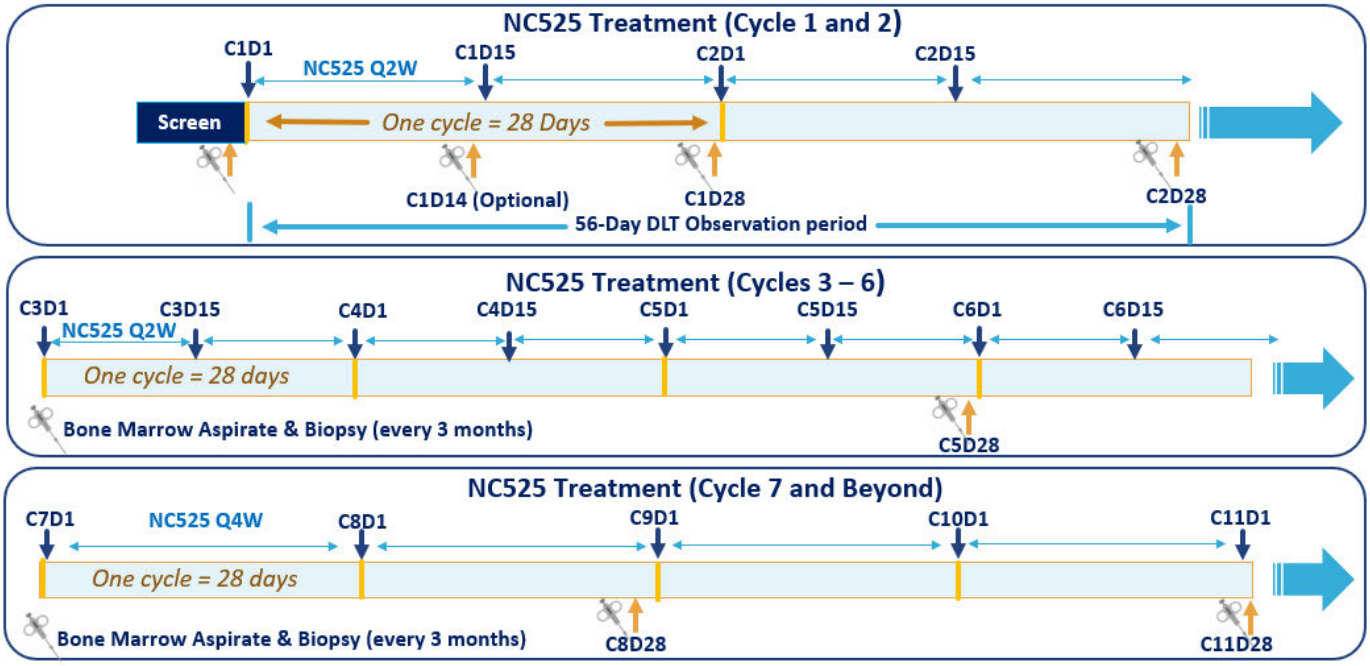
Study Phase and Cohorts

A BOIN design will be utilized to determine the MTD of NC525, where a minimum of 3 evaluable subjects will be enrolled in each dose level from Cohort 2 onwards. In the case of the starting dose level (2mg/kg), a minimum of 1 evaluable subject may be enrolled (in the absence of severe toxicity) prior to determining escalation to the next dose level given the dose is an approximation of the minimally active dose (PD30).

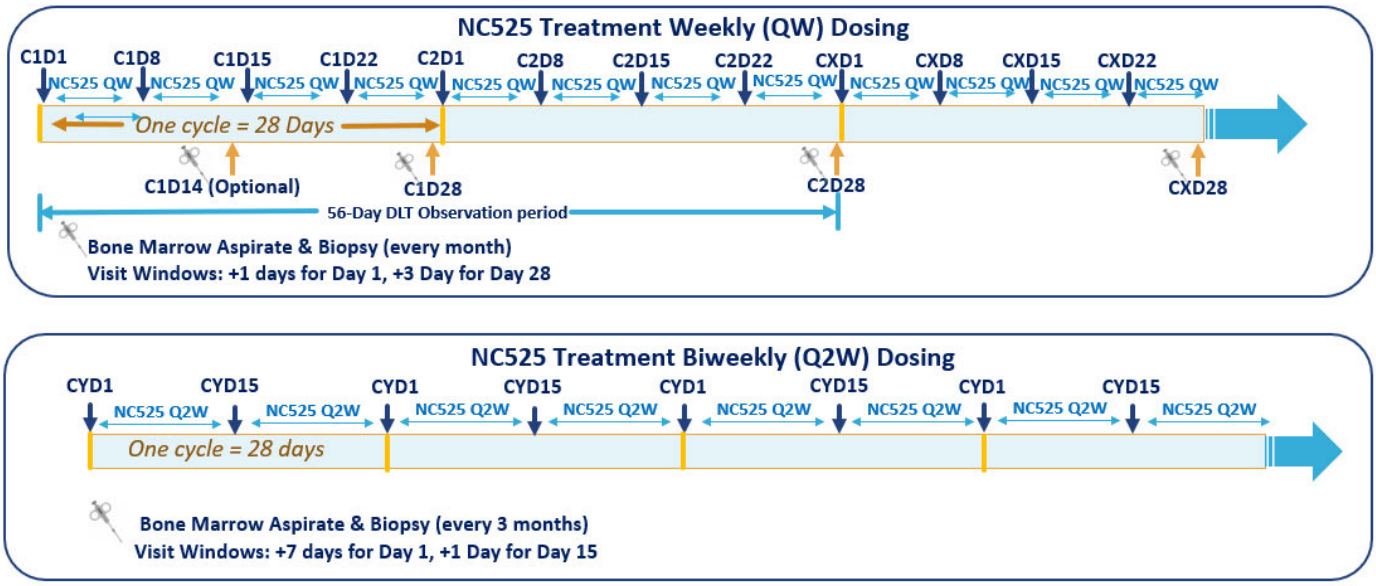
All dose escalation and de-escalation decisions will be based on the occurrence of DLTs at a given dose during the first 56-day period (i.e., first 2 cycles), also referred to as the DLT observation period (Figure S3), and will be made jointly by the Clinical Study Team comprised of the Sponsor (Chief Medical Officer and Medical Monitor), CRO Medical Monitor and Investigators once the minimum number of evaluable subjects (n=3) have completed the DLT observation period.

Figure S3: Phase 1 Study Schema

a. Cohort 1



b. Cohort 2 and Above



A subject is considered evaluable if they have received at least four doses of NC525 and completed the 56-day DLT observation period or discontinued earlier due to an adverse event. Only one subject will be dosed on the first day of dosing for each cohort (additional subjects can begin in ≥ 48 hours). If there are multiple subjects in the screening process at the time the third subject within a cohort begins treatment, additional subjects may be enrolled with approval of the Sponsor using the BOIN design and based on the number of subjects evaluable at the current dose level.

The Escalation/De-escalation Rules per BOIN (Table S1) can be used to help inform decisions during the safety review meetings. Dosing decisions include escalate to the next higher dose, stay at the current dose, de-escalate to the next lower dose, or eliminate the dose level (i.e., unacceptably toxic dose). Dose escalation and de-escalation will be based on the cohort size of 3. That is, no dose escalation will be made before 3 patients are treated at the current dose, except the first dose where the accelerated titration may be performed and a minimum of 1 subject may be enrolled.

To reference the dose finding rules, one can use the number of evaluable subjects in a cohort that have been treated to determine the appropriate action based on the number of subjects who have experienced a DLT as indicated by the column. For example, at a given dose level, if 6 subjects have been enrolled but only 5 evaluable subjects have passed the 56-day DLT observation period, a decision could be made to escalate to the next dose cohort as long as there is ≤ 1 DLT in any of the 5 subjects.

Table S1: Dose escalation/de-escalation rule for the BOIN Design

Escalation/De-escalation Rules													
Action**	Number of evaluable patients treated*												
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Escalate if number of DLT ≤	0	0	0	1	1	1	1	1	2	2	2	2	2
Stay at current dose if number of DLT is equal to	1	1	1	NA	2	2	2	2	3	3	3	3, 4	3, 4
De-Escalate if the number of DLT ≥	2	2	2	2	3	3	3	3	4	4	4	5	5
Eliminate if number of DLT ≥	3	3	3	4	4	4	5	5	6	6	6	7	7

Note: "# of DLT" is the number of subjects with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of subjects.

*A subject is considered evaluable if they have received at least four doses of NC525 and completed the 56-day DLT observation period or discontinued earlier due to an adverse event.

**If de-escalation rule is met at Dose Level 1, alternative dose levels or administration schedules may be considered pending safety review and emerging data.

In addition to the BOIN dose finding rules, decisions to escalate to the next dose will be based on all available PK, PD, efficacy, safety, and tolerability data for the prior cohort(s). Efficacy measures consist of MLFS, CR, CRh, CRi and hematological recovery. Since NC525 targets and effectively kills leukemic blasts and LSC, PD marker comprises clearance of blasts from the marrow and peripheral blood. Further PD marker such as expression of LAIR-1 on blast cells to correlate with response will be assessed.

Two dose levels will be expanded to determine an optimal biologically active RP2D and administration schedule of NC525. After Dose Escalation has been completed, safety expansion up to 14 subjects per dose (including subjects treated at that dose level in the dose escalation phase) will be performed.

The doses for safety expansion are required to be no higher than the MTD and show sufficient PK/PD and anti-leukemic activities. The RP2D will be chosen based on an overall assessment of DLTs, safety profile, subject tolerance, biological activities and clinical efficacy signals collected at all different doses tested. The RP2D is required to be no higher than the MTD. A Bayesian toxicity monitoring rule will be used to ensure safety during safety expansion.

Dose Levels and Cohorts

The Dose Escalation part of the study will begin with the following planned dose levels and cohorts:

- **Dose Level 1**: 2 mg/kg biweekly*
- **Dose Level 2**: 2.5 mg/kg weekly*
- **Dose Level 3**: 4.5 mg/kg weekly*
- **Dose Level 4**: 10 mg/kg weekly*
- **Dose Level 5**: 20 mg/kg weekly*
- **Dose Level 6**: 30 mg/kg weekly*

*Cohort 1: Biweekly (Q2W) for Cycles 1 through 6 followed by every 4 weeks (Q4W) thereafter. For Cohort 2 and Above: Weekly (QW) dosing for Cycles 1 and 2. Subjects may continue weekly (QW) dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to biweekly (Q2W) dosing. For subjects who maintain a weekly dosing schedule, local bone marrow biopsies and aspirates should continue to be collected every 28-days.

The planned dose levels for Dose Escalation include a maximum dose increment of less than a half-log (233%) between each dose level. Using the Escalation/De-escalation Rules governed by the BOIN design, if criteria is met allowing dose escalation, the subsequent dose level will first be evaluated against the Dose Increment Modification Rules For Dose Escalation (Table S2) taking into consideration the number of adverse events (Grade ≥ 2) and dose limiting toxicities which occurred at the current dose level prior to selecting the next dose.

In the event a dose increment modification is indicated during the Dose Escalation phase of the study, an ad-hoc safety meeting will occur with the Clinical Study Team to review the adverse event(s) against the qualifying criteria before any dose modifications are made.

All Adverse Events (excluding AEs unequivocally due to the underlying disease or an extraneous cause) occurring during the DLT Observation Period will be evaluated against the Dose Increment Modification rules, as follows:

- Limit the maximum dose increment to 100% if patients of a given cohort experience one Grade ≥ 2 AE during the DLT period.
    - ***Example**: If one ≥ Grade 2 AE occurs in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 100% (4mg/kg) instead of the originally planned dose of 4.5mg/kg.*

- Limit the maximum dose increment to 50% if patients of a given cohort experience two or more Grade ≥ 2 AEs during the DLT period.
    - ***Example:** If two or more ≥ Grade 2 AE occurs in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 50% (3mg/kg) instead of the originally planned dose of 4.5mg/kg.*

- Limit the maximum dose increment to 50% if patients of a given cohort experience one DLT during the DLT period.
    - ***Example**: If one DLT occurs in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 50% (3mg/kg) instead of the originally planned dose of 4.5mg/kg.*

- Limit the maximum dose increment to 30% if patients of a given cohort experience two DLTs during the DLT period.
    - ***Example**: If two DLTs occur in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 30% (2.6mg/kg) instead of the originally planned dose of 4.5mg/kg.*

Table S2: Dose Increment Modification Rules for Dose Escalation

Dose Cohort	Planned Dose (mg/kg)	Frequency*	Dose Increment Modification During DLT Observation Period				
			If No DLT and/or no Grade ≥ 2 AE[a] in a given cohort	If one Grade ≥ 2 AE[a] in a given cohort	If two or more Grade ≥ 2 AEs[a] in a given cohort	If One DLT in a given cohort	If 2 DLTs in a given cohort
1	2	Q2W	Dose increment as planned	Maximum dose increment to 100%	Maximum dose increment to 50%		Maximum dose increment to 30%
2	2.5	QW					
3	4.5	QW					
4	10	QW	Dose increment as planned				
5	20	QW	Dose increment as planned				
6	30	QW	Dose increment as planned		Dose increment as planned		

a Adverse events (except for AEs unequivocally due to the underlying disease or an extraneous cause) occurring during the DLT Observation Period will be evaluated against the Dose Increment Modification rule.

*Cohort 1: Biweekly (Q2W) for Cycles 1 through 6 followed by every 4 weeks (Q4W) thereafter. For Cohort 2 and Above: Weekly (QW) dosing for Cycles 1 and 2. Subjects may continue QW dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to Q2W dosing.

CLINICAL DEVELOPMENT PLAN

Target Population for First in Human Trial

Men and women, 18 years or older subjects with Advanced Myeloid Neoplasms. Subjects must provide written informed consent and have adequate organ function. Subjects must consent to have a fresh bone marrow aspirate and biopsy prior to entering the study and during treatment. Subjects with certain serious medical conditions (in addition to the diagnosis of AML or MDS or CMML) would be excluded from participation in the trial.

ELIGIBILITY CRITERIA

Inclusion Criteria:

Participants are eligible to be included in the study only if all of the following criteria apply:

1) The subject is willing to provide written informed consent for the trial.
2) Be ≥ 18 years of age on the day of signing informed consent.
3) Subject has one of the following Myeloid Neoplasms determined by pathology review at the treating institution:
    - Relapsed or Refractory AML,

      Note: Active, relapsed, or refractory AML is defined as any one of the following:
        - Primary induction failure, or (PIF) after 2 or more cycles of therapy,
        - First early relapse after a remission duration of fewer than 6 months,
        - Relapse refractory to salvage combination chemotherapy second or subsequent relapse, or
        - Relapsed or refractory AML with at least 5% blasts by bone marrow biopsy or aspirate, or at least 1% blasts in peripheral blood.
    - Relapsed or Refractory Myelodysplastic syndrome (MDS) after prior hypomethylating agents.

      Note: Subject must have sub-type MDS-EB2 with 10-19% blasts by bone marrow biopsy or aspirate.
    - Relapsed or Refractory Chronic myelomonocytic leukemia (CMML) with progressive disease or lack of response to hypomethylating agents.
4) A male subject must agree to use approved contraception (based on institutional guidelines) and refrain from sperm donation or expecting to father a child, from Screening through the treatment period and for at least 90 days after the last dose of study treatment.
5) A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP);
    b. A WOCBP agrees to follow approved contraceptive guidance (based on institutional guidelines) from Screening through the treatment period and for at least 90 days after the last dose of study treatment.
6) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
7) Life expectancy greater than or equal to 12 weeks as judged by the Investigator.
8) Have adequate organ function as defined in the following table (Table S3).

Table S3: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematology	
Peripheral white blood cell (WBC)	≤ 25,000/μL[1]
Renal	
Measured or calculated[2] creatinine clearance	Creatinine clearance > 60 mL/min
Hepatic	
Total bilirubin	<1.5 × ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 × ULN. **Note:** Subjects with documented Gilbert's syndrome with elevated baseline total bilirubin ≤ 3.0 mg/dL or indirect hyperbilirubinemia suspected to be result of hemolysis may be enrolled.
AST (SGOT) and ALT (SGPT)	≤ 3.0 × ULN

ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[1] Hydroxyurea or cytarabine therapy is allowed to reduce white blood cells to meet this inclusion criterion. White blood cells should be determined ≥ 24 hours after the last leukoreduction therapy administration. Final leukoreduction therapy administration should not be administered ≤ 3 days prior to the first dose of NC525 without medical monitor approval.

[2] Creatinine clearance (CrCl) should be calculated per institutional standard. GFR can also be used in place of creatinine or CrCl.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Note: Screening labs must be collected within 7 days prior to the start of study treatment.

<u>Exclusion Criteria</u>:

Participants are excluded from the study if any of the following criteria apply:

1) Has a diagnosis of acute promyelocytic leukemia (M3, APL), accelerated phase or blast crisis of chronic myeloid leukemia.
2) History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.

3) Patients with active Central Nervous System (CNS) involvement (such as leukemic infiltration, blast in the spinal fluid, or subjects with extramedullary disease).
4) A WOCBP who has a positive pregnancy test (within 72 hours) prior to treatment.
5) History or evidence of any other clinically significant disorder, condition or disease (e.g., symptomatic congestive heart failure, unstable angina pectoris, symptomatic myocardial infection, uncontrolled cardiac arrhythmia, pericardial disease or heart failure New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity and in the opinion of the Investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion.
6) Chronic respiratory disease or any other medical condition that requires continuous oxygen that in the opinion of the Investigator, would adversely affect his/her participation in this study.
7) Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention.

   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
8) Is currently participating in or has participated in a study of the following prior to the first dose of study treatment:
   a. An investigational biologic or an investigational device within 4 weeks or 5 half-lives (whichever is longer);
   b. An investigational oral agent within 2 weeks or 5 half-lives (whichever is shorter).

   Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as the specified washout period has been completed.
9) Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior chemotherapy, immunotherapy and radiation therapy) and/or complications from interventions before starting therapy.

   Note: Subjects with stable chronic conditions (≤ Grade 2) not expected to resolve (such as neuropathy and alopecia) are exceptions and may still enroll.
10) Has previously had an allogeneic solid organ transplant.
11) Autologous HSCT within 6 weeks before the start of study treatment.
12) Allogeneic HSCT within 6 months before the start of study treatment.
13) Any active acute or chronic graft-versus-host disease (GvHD), grade 2-4, or active chronic GvHD requiring systemic treatment.
14) Any systemic therapy (e.g. calcineurin inhibitors (CNI), steroids, etc.) against GvHD within 4 weeks before the start of study treatment.

15) Any Grade ≥ 2 persistent non-hematological toxicity related to allogeneic transplant, such as those requiring systemic immunosuppressive therapy.

16) Previous CAR-T therapy.

17) Known concurrent malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry after treatment with curative intent.

Note: Cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year are not considered exclusionary.

18) Has severe hypersensitivity (≥ Grade 3), known allergy or reaction to Immunoglobulins or NC525, and/or any of their excipients.

19) Uncontrolled systemic fungal, bacterial, viral, or other infection despite appropriate anti-infection treatment at the time of eligibility confirmation.

20) Has a known history of HIV infection. **Note**: No HIV testing is required unless mandated by the local health authority.

21) Has a known active chronic hepatitis B infection or chronic hepatitis C infection with the exception of those with an undetectable viral load within 3 months.

22) Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate, in the opinion of the treating investigator.

23) Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.

STUDY DRUG ADMINISTRATION AND TREATMENT SCHEDULE

For Cohort 1, NC525 is given by Intravenous (IV) infusion every two weeks (on Days 1 and 15 of each cycle) for the first 6 cycles. For subjects who continue on treatment beyond Cycle 6, NC525 will be administered every 4 weeks (on Day 1 of each cycle only).

For Cohort 2 and above, NC525 will be administered every week on Days 1, 8, 15 and 22 during Cycles 1 and 2. Subjects may continue weekly dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to biweekly dosing. For biweekly dosing, NC525 will be administered every two weeks on Days 1 and 15 of each cycle. Subjects who derive clinical benefit may continue to receive NC525 for a total of 2 years or until the criteria for discontinuation of treatment are met (whichever comes first).

Each cycle will be 28-days in duration. A detailed description of the treatment schedule is included below (Table S4):

Table S4: NC525 Treatment Schedule

a. Cohort 1

Dosing Schedule													
Frequency	**Q2W**												**Q4W**
Cycle	**1**		**2**		**3**		**4**		**5**		**6**		**7+**
Day	1	15	1	15	1	15	1	15	1	15	1	15	1

b. Cohort 2 and Above

Dosing Schedule						
Frequency	**Weekly (QW)***				**Biweekly (Q2W)**	
Window	+1 day				+7 days	+1 day
Day	1	8	15	22	1	15

* Subjects may continue QW dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to Q2W dosing.

Alternate dose levels and administration schedules, including ramp-up to target dose, may also be explored depending on PK, pharmacodynamic (PD), biomarkers, safety results, and feedback from investigators.

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Abbreviation or Specialized Term	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase (also called SGPT)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase (also called SGOT)
AUC	Area Under the Curve
BM	Bone Marrow
bpm	Beats per Minute
BSA	Body Surface Area
CLL	Chronic Lymphocytic Leukemia
C_{max}	Maximum Concentration of Drug
CMML	Chronic myelomonocytic leukemia
CNS	Central Nervous System
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CR	Complete Response
CRh	Complete Remission with partial hematologic recovery
CRi	Complete Remission with Incomplete Blood Count Recovery
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CS	Clinically Significant
CTACE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte–Associated Protein 4
DC	Dendritic cell
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
EC_{30}	Effective Concentration for 30% of Maximum Effect

Abbreviation or Specialized Term	Definition
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-Free Survival
EOT	End-of-Treatment
ESA	Erythropoietin-Stimulating Agent
FAAN	Food and Allergy Anaphylaxis Network
FAS	Full Analysis Set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FIH	First-in-Human
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practices
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating agent
HNSTD	Highest Non-Severely Toxic Dose
HPV	Human Papillomavirus
HR	Hematologic Response
hr	Hours
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
IBW	Ideal Body Weight
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee

Abbreviation or Specialized Term	Definition
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalized Ratio
INs	Investigator Notifications
irAE	Immune-Related Adverse Event
IRC	Independent Review Committee
IRB	Institutional Review Board
iv	Intravenous
LAIR	Leukocyte-Associated Immunoglobulin-like Receptor
LDH	Lactate Dehydrogenase
LTLS	Laboratory Tumor Lysis Syndrome
LKA	Last Known Alive
LPS	Lipopolysaccharide
mAb	Monoclonal Antibody
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
MLFS	Morphologic Leukemia-free State
MNTD	Maximum Number of Tolerated Doses
MR	Morphologic Relapse
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NIAID	National Institute of Allergy and Infectious Disease
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
ORR	Overall Response Rate
OR	Objective Response
OS	Overall Survival

Abbreviation or Specialized Term	Definition
PAD	Pharmacologically Active Dose
PAS	PK Analysis Set
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Protein Ligand 1
PEF	Peak Expiratory Flow
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Remission
PT	Prothrombin Time
QTcF	QT interval measurement corrected by Fridericia's formula.
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
R/R	Relapse/Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SSD	Safe Starting Dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-Life
TEAE	Treatment-Emergent Adverse Event
TK	Toxicokinetic
TLS	Tumor Lysis Syndrome
TTP	Time to Progression
TME	Tumor Microenvironment
TPS	Tumor Proportion Score
Treg	Regulatory T cell
ULN	Upper Limit of Normal

Abbreviation or Specialized Term	Definition
US FDA	United States Food and Drug Administration
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This is an open-label, non-randomized, Phase 1 study to determine the safety and tolerability of NC525. This study will also assess the clinical benefit in subjects with advanced myeloid neoplasms. The study will be conducted in 2 parts, Dose Escalation and Safety Expansion. The safety and tolerability of NC525 will be evaluated by exploring escalating dose levels of NC525. In addition, the pharmacologically active dose (PAD), maximum tolerated dose (MTD), and minimally active dose (MAD) of NC525 will be determined. Once the MTD is achieved or the highest dose cohort is completed without the MTD, the safety and tolerability will be further assessed through expansion of a few dose levels to determine an optimal Recommended Phase 2 Dose (RP2D) and administration schedule of NC525.

1.1. Background

1.1.1. Pharmaceutical and Therapeutic Background

NC525 is a humanized immunoglobulin gamma 1, kappa (IgG1κ) monoclonal antibody specific for Leukocyte Associated Immunoglobulin Like Receptor 1 (LAIR-1) protein that is being developed for the treatment of acute myeloid leukemia (AML). LAIR-1 is a member of both the immunoglobulin superfamily and the leukocyte-associated inhibitory receptor family. Its genetic locus maps to a region of 19q13.4 called the leukocyte receptor cluster, which contains at least 29 genes encoding leukocyte-expressed receptors of the immunoglobulin superfamily. LAIR-1 has been identified as an anchor for tyrosine phosphatase SHP-1. While LAIR-1 is exclusively expressed on immune cells, its expression is aberrantly elevated on AML cells. High LAIR-1 expression on leukemic stem cells from AML patients and its absence on normal hematopoietic stem cells (HSCs) make it a unique and attractive target for a novel AML therapy.

LAIR-1 regulates the immune system by binding to extracellular ligands that possess collagenous structures and delivering a signal to immune cells via a cytoplasmic tail containing two immunoreceptor tyrosine-based inhibition motifs (ITIMs). Endogenous LAIR-1 ligands identified to date include collagen, complement protein C1q, Surfactant Protein-D (SP-D), Mannose Binding Lectin (MBL), and Colec12. When LAIR-1 is activated by binding to its ligand, both ITIMs are phosphorylated, and SHP-1 phosphatases are recruited and phosphorylated to trigger immune-inhibitory signaling in healthy immune cells. In AML, LAIR-1 functions to promote leukemia cell stemness and disease progression via the recruitment of SHP-1 but signaling occurs through a phosphatase independent SHP-1 pathway. NC525 binds to LAIR-1 with higher affinity than natural ligands and induces LAIR-1 ligation dependent cell death of AML cells.

NC525 binds human LAIR-1 with an affinity of 2.27 nM and causes AML cell death primarily by inducing LAIR-1 receptor mediated signaling pathways in AML cells. NC525 restricted leukemic tumor growth of human MV4-11, and THP-1 AML in cell line-derived xenograft (CDX) models. In patient-derived xenograft (PDX) models, the disease progression and tumor burden of the patient-derived AML PBMCs implanted in NSG-SGM3 mice were decreased by NC525 treatment. This anti-tumor activity was observed in multiple experiments utilizing patient-derived blasts from AML patients. NC525 also inhibited colony formation of patient-derived leukemic stem cells in an in vitro assay but did not affect colony formation of normal HSCs.

NC525 does not function as a check point inhibitor. NC525 did not affect normal immune cells from $CD34^+$ cord blood cells reconstituted in an NSG-SGM3 murine model. In a human

lymphocyte-replete CDX model NC525 treatment effectively reduced disease progression compared to animals treated with isotype, but NC525 had no effect on total numbers of T cells or B cells in the spleen, bone marrow, or blood, nor did NC525 alter T-cell activation status as measured by CD25 expression, suggesting NC525 does not function as a checkpoint inhibitor.

Leukemias are malignant blood disorders characterized by uncontrolled overproduction of hematopoietic progenitors in acute leukemias or terminally differentiated leukocytes in chronic leukemias. Acute myeloid leukemia (AML) is the most common adult acute leukemia, whereas acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Extensive research has led to the recent approval of novel therapies in AML. However, the mainstay of treatment in AML has remained unchanged since the 1970s. Therefore, there is a significant unmet need for AML patients that fail to respond to or relapse after standard-of-care (SOC) treatments, including allogeneic stem cell transplantation and targeting actionable mutations. In addition, a significant fraction of SOC patients relapses due to the persistence of chemotherapy-resistant leukemia stem cells (LSCs) or immune evasion. Therefore, identifying unique therapies that target elusive LSCs and promote immune responses to AML to prevent relapse is highly sought after. Furthermore, since AML progenitors and normal myeloid progenitors share similar expression of cluster of differentiation (CD) markers, it is crucial to differentiate LSCs from HSCs and their normal progenitors to lessen or prevent cytopenia and other adverse side effects.

LAIR-1 has been reported as a cell surface marker of acute lymphoblastic leukemia (ALL), and higher expression of LAIR-1 correlates with worse clinical outcomes (Yousef Alrayes et al. 2019). Deletion of LAIR-1 in mouse BCR-ABL1 B cell leukemia cells led to cell death in vitro and disease remission within a leukemia transplant mouse model (Chen et al. 2015). Taken together, these data suggest that LAIR-1 may play a similar role in promoting ALL development through dominant oncogenic signaling pathways.

In myeloid neoplasms, LAIR-1 expression is aberrantly high on AML blasts and LSCs, Myelodysplastic Syndrome (MDS) blasts and monocytes, and myelo-monoblasts of Chronic Myelomonocytic Leukemia.

Our analyses have shown that LAIR-1 is preferentially expressed in LSCs and leukemic progenitors compared to HSCs and progenitors. Furthermore, Galen et al. have shown from a combination of transcriptomics and mutational analyses in single cells from AML patients, the existence of distinct functional subsets and their associated drivers (van Galen et al. 2019). This difference may explain the preferential killing of leukemic blasts and LSCs by NC525 with sparing of normal hematopoietic cells in preclinical studies, including *in vitro* CFU assays and *in vivo* in both CDX and PDX models.

It has been reported that LAIR-1 functions to promote leukemia cell stemness and disease development via recruitment of Src Homology Region-1 (SHP-1) (Kang et al. 2015). Ligands containing collagen-like domains activate LAIR-1 to subsequently trigger downstream signaling molecules CAMK1 and CREB (Kang et al. 2015) which have been implicated in sustaining AML stem cell activity (Kang et al. 2015; Kang et al. 2016). LAIR-1 knockdown increases the cell death of leukemia cells (Kang et al. 2015). Interestingly, our data support a model in which enhanced LAIR-1 signaling by NC525 receptor ligation drives apoptotic signaling and cell death in AML cells.

In summary, NC525, a LAIR-1 specific mAb being developed as a treatment for AML, has demonstrated potent activity against AML in several CDX and PDX models of disease. In addition,

these studies support the unique ability to spare normal stem cells and immune cells while simultaneously targeting and killing AML blast and leukemia stem cells through LAIR-1 ligation-mediated cell death. The FIH study, NC525-01, will evaluate NC525 among patients with advanced myeloid neoplasms.

1.1.2. Pharmacokinetics of NC525

The pharmacokinetics (PK) of NC525 were studied in a single dose, dose-range finding (DRF) study, and a repeat dose Good Laboratory Practice (GLP) study.

In the DRF study, NC525 serum concentration-time data following a single 0.5 h intravenous (IV) infusion was evaluated in four dose cohorts that ranged from 0.5 to 85 mg/kg in male and female cynomolgus monkeys. Two female monkeys dosed in the two lowest dose cohorts developed anti-drug antibodies (ADA,) which resulted in a rapid clearance of NC525 from the system. Since only partial toxicokinetic (TK) was useful for these animals, they were excluded from TK analyses. In animals which did not develop ADA, NC525 remained quantifiable until the end of the study (504 h) following dosing. The concentration-time profiles of serum NC525 were characterized by a bi-phasic decline with time. Serum concentrations and TK parameters of NC525 within and between genders were generally comparable and within the expected biological variation. Serum maximum concentration (C_{max}) of NC525 was observed at the end of infusion (t_{max} =0.5 h) except for animals dosed with 27.5 mg/kg NC525, which was 2 h. Serum C_{max} and the area under the curve (AUC) of NC525 remained mostly dose proportional across doses and genders. Most of the circulating NC525 found in serum at C_{max} disappeared during the rapid phase of elimination within 96 h; the rest was cleared afterward, during the terminal phase of elimination. The initial and terminal half-life (T½) of NC525 ranged between 3.4-11.5 and 151-248 h, respectively, except for 0.5 mg/kg male, which was 341 h. Two apparent volumes of distribution of the two compartments, central (serum) and the tissue compartments (Vc,compt and Vt,compt), were 0.13-0.20 and 0.08-0.12 mL/kg. Vc,compt and Vt,compt) were 0.13-0.20 and 0.08-0.12 mL/kg. The apparent volume of distribution at steady state (Vss) were 0.22-0.29 mL/kg. The combined Vss were 0.22-0.29 mL/kg. The combined clearance (Cl) of NC525 was 0.004-0.013 mL/h/ kg. The mean residence time (MRT) of NC525 was between 211 and 480 h in male and 205 and 337 h in female monkeys.

A weekly dosing regimen was selected for the GLP repeat dose study to enable a weekly or bi-weekly dosing regimen in the Phase I clinical trial. NC525 serum concentration-time data following a weekly dosing of 0, 2, 20, and 100 mg/kg over 0.5 h by IV infusion in male and female cynomolgus monkeys were determined after the first (Day 1) and last dose (Day 29). NC525 serum concentrations were below the lower limit of quantitation (LLOQ = 1500 ng/mL) in all pre-dose samples obtained from treated animals on Day 1 and from all 0.5-hour post start of infusion (SOI) samples analyzed from control animals on Day 29.

Systemic exposure to NC525 appeared to be independent of sex. There were no consistent differences in individual serum concentrations, C_{max}, and AUC values between males and females; therefore, the following discussion is based on combined data for males and females. NC525 was quantifiable up to 168 hours post SOI on Day 1 and up to 24 hours post SOI (the last timepoint for main study animals) or 240, 504, 672, and 840 hours post SOI at 2 mg/kg and up to 24 hours post SOI (the last timepoint for main study animals) or 1176 hours post SOI at 20 and 100 mg/kg on Day 29. Median NC525 T_{max} values were observed by 0.5 hours post SOI on Days 1 and 29 (median values could not be reported at 2 mg/kg on Day 29 or at 20 mg/kg on Day 1 due to not being an actual collection time point). Individual NC525 T_{max} values ranged from 0.5 to 2.33 hours

post SOI at 2 mg/kg, 0.5 to 8 hours post SOI at 20 mg/kg, and from 0.5 to 2 hours post SOI at 100 mg/kg. Following once weekly IV infusion administration of NC525, mean C_{max}, $AUC_{0\text{-}24hr}$, and $AUC_{0\text{-}168hr}$ values for NC525 increased with increasing dose in an approximately dose proportional manner on Days 1 and 29.

Systemic exposure ($AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}168hr}$) to NC525 appeared to generally increase (~2-fold) following repeated administration of NC525. On Day 29, mean $T_{1/2}$ values were 133, 262, and 255 hours at 2, 20, and 100 mg/kg and mean Cl values were 0.410, 0.255, and 0.256 mL/hr/kg at 2, 20, and 100 mg/kg.

All animals that were evaluated for ADA were negative at pretest, pre-dose on Days 15 and 29, and at recovery, with the exception of 1 male and 1 female at 20 mg/kg, which were confirmed positive at recovery (titers of 1:8 and 1:80, respectively). These animals were not excluded from the TK analysis.

1.1.3. Pharmacology of NC525

The pharmacology of NC525 has been studied in a variety of *in vitro*, *ex vivo*, and *in vivo* systems to support its use as an investigational drug in oncology.

LAIR-1 regulates the immune system by binding to extracellular ligands and delivering a signal to immune cells via a cytoplasmic tail containing two ITIMs. When LAIR-1 is activated by binding to its ligand, both ITIMs are phosphorylated to trigger immune signaling, which, in AML, functions to promote leukemia cell stemness and disease progression. NC525 binds to LAIR-1 with a much higher affinity than its natural ligands and induces LAIR-1 ligation dependent cell death of AML cells. The ability of NC525 and its parent molecule 11B3.IgG1 to inhibit AML cell growth and survival was tested in a series of non-clinical studies summarized below.

NC525 binds human LAIR-1 with an affinity of 2.27 nM and causes AML cell death primarily by inducing LAIR-1 receptor mediated signaling pathways in AML cells. In multiple CDX and PDX mouse models, NC525 exhibited potent anti-leukemic activity. NC525 restricted leukemic tumor growth of human MV4-11 and THP-1 cells in CDX models. In PDX models, the disease progression and tumor burden caused by patient-derived leukemic stem cells implanted into NSG-SGM3 mice was significantly decreased by NC525 treatment. This anti-tumor activity was observed in multiple independent experiments utilizing bone marrow derived from different AML patients. NC525 also inhibited colony formation of patient-derived leukemic stem cells *ex vivo* but did not affect colony formation of normal HSCs. Likewise, NC525 did not affect normal immune cells from $CD34^+$ cord blood cells reconstituted in an NSG-SGM3 murine model. Finally, in a secondary transplant model, recipient mice engrafted with bone m arrow from NC525-treated PDX mice did not develop disease, unlike mice engrafted with bone marrow from control-treated PDX mice, indicating that NC525 targets and kills leukemic stem cells within the bone marrow.

In summary, these collective data suggest that NC525 may be a promising agent to treat AML malignancy with the advantage of specifically destroying leukemic stem cells and sparing the normal HSCs.

1.1.4. Non-Clinical Safety and Potential Risks of NC525

The toxicology of NC525 has been studied in a variety of *in vitro* and *in vivo* systems to support its use as an investigational drug in leukemia.

NC525 treatment of healthy blood leukocytes did not elicit cell death nor cytokine release *in vitro*, nor did administration of NC525 in humanized mice impact leukocyte retention, T cell proliferation, or anti-leukemic activity. These data are described in the NC525 Investigator Brochure (IB).

A GLP toxicity study in which cynomolgus monkeys were administered escalating doses of NC525 revealed no adverse effects. The most notable findings were a moderate to a marked reduction in NK cell counts in male monkeys at the highest dose cohort, 100 mg/kg, and an inflammatory response in one male animal in the high dose group, which could not be directly attributed to NC525. No clinical or veterinary findings were associated with the decrease in NK cells. The highest dose administered, 100 mg/kg, was identified as the NOAEL and HNSTD. Complete results of this study and dose-finding studies are described in the NC525 IB.

1.2. Study Rationale

1.2.1. Rationale for the Safe Starting Dose

The safety of NC525 was assessed in two studies, a single dose range finding study and a repeat dose 28-day GLP-compliant study (5 doses, weekly). In the DRF study, NC525 was administered at four different dose levels ranging from 0.5 to 85 mg/kg and in the GLP study at, 2, 20, and 100 mg/kg. There were no test article-related effects on body weight, food consumption, coagulation, or urinalysis in either the DRF or the repeat dose GLP study.

Test article-related effects on hematology parameters in the DRF study were limited to minimally decreased red blood cell (RBC) count, hemoglobin, and hematocrit in the 85 mg/kg group female at Day 3 with complete reversibility at Day 22. In the GLP study, mild reduction in RBCs in males administered 100 mg/kg was also observed at Day 31. The changes in RBC mass parameters were not accompanied by alterations in other erythrocyte parameters in either study. A mild reduction in neutrophils was also noted in one female dosed at 100 mg/kg in the GLP study. This individual also had a lower neutrophil count at second pretreatment, and a similar magnitude of decreased neutrophil count was observed in a control male on Day 31. Therefore, the decrease in the neutrophil count was considered not likely related to NC525 treatment.

In the GLP study, cynomolgus male monkeys that received 100 mg/kg/dose, had NC525-related decreases in CD45+CD159a+ cell counts (NK cells) evaluated by immunophenotyping, that persisted through the recovery period. Additionally, one male at 100 mg/kg/dose had evidence of an inflammatory response (minimal to mild increases in Döhle bodies, fibrinogen, and globulin with mild decreases in albumin and albumin/globulin ratio) and mild decreases in RBC mass parameters (erythrocyte count, hemoglobin concentration, and hematocrit) at the end of the dosing period, which had resolved following the recovery period. Due to the unique occurrence (1 out of 10 monkeys) in this animal at the highest dose level, with a resolution during the non-dosing recovery period, these changes were of uncertain relation to NC525 administration.

Test article-related effects on clinical chemistry parameters were limited to minimally decreased glucose concentration in the 27.5 and 85 mg/kg group males at Day 22 of the DRF study. No dose dependent changes in glucose were observed in the repeat dose study.

In conclusion, administration of NC525 by intravenous infusion to cynomolgus monkeys was well tolerated at all doses up to 100 mg/kg.

The no observed adverse effect level (NOAEL) in monkeys was defined as 100 mg/kg. The peak plasma levels observed after 5 doses of 100 mg/kg every week were used as the safety threshold.

Serum concentration profiles in monkeys were fit to a population PK model, which was scaled to predict human concentrations. Single species allometric scaling was applied for an average healthy adult weight of 80 kg as published (Wang et al. 2016) where 0.85 was applied as an exponent for the human to monkey weight ratio on clearance and no exponent was applied to the weight ratio on other parameters. The simulated peak serum concentrations were compared to the safety threshold, and a factor of 0.85 was estimated to define the Human Equivalent Dose (HED). Therefore, 100 mg/kg correspond to a HED of 85 mg/kg, and this is considered the NOAEL in human for the purposes of dose definition.

The rationale for the proposed Phase 1 starting dose has considered all relevant preclinical pharmacology, toxicology data, and anti-leukemic effects in murine AML models.

NC525 is well-tolerated, and repeated administration of dosages 50-fold higher (on a mg/kg basis) than the planned clinical starting dose were not associated with any adverse toxicities.

A risk assessment for NC525 was performed to support dose selection. Relevant factors for NC525 are discussed below.

The rationale for the proposed Phase 1 safe starting dose (SSD) of 2 mg/kg is based on combined preclinical pharmacology and toxicology data, including anti-leukemic responses in murine AML models. The FDA Guidance for Industry Estimating the Maximum Safe Starting Dose (SSD) in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers was used.

The effectiveness results from CDX murine models were integrated to calculate the doses that lead to 30% (PD30 0.72 mg/kg), 50% (PD50 1.7 mg/kg) and 90% (PD90 15.3 mg/kg) of the maximum effect. Serum concentrations in mice were fit to a PK model, which was used to simulate the exposures in mice after multiple dosing. Simulations of 6 doses administered once weekly in 20 gram (healthy) mice were performed to predict the exposures in CDX murine models under the assumption of equivalence in PK with healthy mice. The median simulated trough concentrations (minimum concentration at the end of the dosing interval) at the 3 dose levels were used to approximate efficacy thresholds.

Single species allometric scaling was used to derive human pharmacokinetic parameters from Cynomolgus monkeys' pharmacokinetics. The human PK model was used to simulate serum concentrations at different doses administered every two weeks, and the 95% CI of the simulated human trough values were compared to the simulated efficacy thresholds in mice. The comparison led to the conclusion that 2 mg/kg every two weeks in humans would lead to the majority of subjects with trough levels slightly above the median CDX mouse PD30 trough levels and a 5 mg/kg dose would lead to the majority of subjects with a trough levels above the determined PD50. A dose of 30 mg/kg is predicted to result trough levels comparable to the PD90 identified from the CDX murine model.

Therefore, the proposed planned dosing rationale is summarized, incorporating dose increment to less than a half-log (233%) between each dose level, as follows:

- Dose Level 1: 2 mg/kg as an approximation of the minimally active dose (PD30)
- Dose Level 2: 4.5 mg/kg as an approximation of PD50
- Dose Level 3: 10 mg/kg to support the characterization of the dose effect curve

- Dose Level 4: 20 mg/kg to support the characterization of the dose effect curve
- Dose Level 5: 30 mg/kg as an approximation of PD90

The proposed dosing scheme provides a starting dose that is expected to minimize safety risks and has the potential to provide clinical benefit, which is ethically important in an oncology trial, especially in myeloid neoplasms including relapsed refractory AML, MDS, and CMML. In the absence of dose-limiting toxicity, the maximum dose that may be explored in the first in human trial will be 30 mg/kg, which is approximately 3-fold lower than the HED of the NOAEL (100 mg/kg) determined by the 5-week GLP-compliant repeat-dose tox study in cynomolgus monkeys. Overall, the dose levels proposed should allow the initial characterization of a dose response curve in patients.

1.2.2. Rationale of Disease Selection for Phase 1 Study

NC525 has been extensively studied in AML and shows promising pre-clinical results, notably targeting LSCs while sparing HSCs. Therefore, it is naturally appropriate to start the FIH dosing in AML.

NC525 has no effects on solid tumors based on pre-clinical models. Therefore, it is not feasible to do a FIH dose escalation study in solid tumors to define a recommended dose for AML. In addition, relapsed refractory Chronic myelomonocytic leukemia (CMML) and MDS were chosen for FIH dosing since CMML and MDS are relatively slowly progressing myeloid malignancies.

1.2.3. Rationale for Efficacy Endpoints

The goal of AML treatment is to control and, ideally, to eradicate disease. Being a Phase 1 study, the primary endpoint is safety and tolerability. Because of its sparing effect on normal HSCs, the aim is also to decrease the incidence of cytopenia-related complications.

Efficacy will be assessed as a secondary endpoint and will include Objective Response (OR), Event-free survival (EFS), and Overall survival (OS).

Efficacy measures for AML have been well established. The European Leukemia Net (ELN) has recently updated the guidelines on response criteria in AML (See Section 1.2.3.1 Response Criteria). Ideally, the purpose of an induction therapy is to achieve complete remission (CR). Once the CR is achieved, further therapies are given as consolidation and/or maintenance to deepen the remission and maximize response duration. However, since NC525 has not been tested in humans, despite its potential to eradicate leukemic stem cells from pre-clinical studies, there is understanding that transplant eligible patients will likely undergo allogeneic stem cell transplant at the discretion of the treating investigator. Assessing optimal value of the study drug will come from observing treatment effect of NC525 in patients who are ineligible for allogeneic stem cell transplant (SCT).

1.2.3.1. Response Criteria for Disease Assessment

Disease Assessments will be performed using the European Leukemia Net (ELN) Guidelines (Döhner et al. 2022) as outlined in the Schedule of Study Procedures (Table 7) and Appendix 6 for the ELN Outcome Measures.

Criteria for Efficacy Measures evaluation are as follows (Döhner et al. 2022):

- Complete Remission (CR): Absolute neutrophil count > 1,000/μL , platelets ≥ 100,000/μL, red cell transfusion independence, and bone marrow with < 5% blasts.
- CR with partial hematologic recovery (CRh): Absolute neutrophil count > 500/μL, platelets ≥ 50,000/μL, otherwise all other CR criteria are met.
- Complete Remission with Incomplete Blood Count Recovery (Cri): Bone marrow with less than 5% blasts, and absolute neutrophils of < 1,000/μL or platelets < 100,000/μL.
- Partial Remission (PR): All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
- Morphologic Leukemia-free State (MLFS): Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of blasts with Auer rods, absence of circulating blasts, absence of extramedullary disease, no hematologic recovery required.
- No Response: Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS or PR are categorized as having no response prior to the response landmark. Patients failing to achieve response by the designated landmark are designated as having refractory disease.
- Non-evaluable Response: Non-evaluable for response will include patients lacking an adequate bone marrow response evaluation. This category will include patients with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment

Response should be based on the most recent bone marrow and hematology panel values. For subjects who require a delay in study treatment for peripheral blood count recovery after a bone marrow evaluation, hematology panel values for 2 weeks from the bone marrow analysis can be used to determine the ELN response. As a significant number of the subjects in this study may have antecedent hematologic illnesses, hematologic response will also be evaluated.

1.3. Research Hypotheses

Treatment with NC525, a humanized immunoglobulin gamma 1, kappa (IgG1κ) monoclonal antibody specific for LAIR-1, will, specifically kill leukemic cells while sparing healthy cells in both the bone-marrow and the periphery, ameliorating disease with minimal toxicity, and resulting in clinical benefit for subjects with advanced myeloid neoplasms.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. STUDY OBJECTIVES

2.1.1. Primary Objectives

1) To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of NC525
2) The recommended Phase 2 dose (RP2D) of NC525 will be defined in subjects with advanced myeloid neoplasms
3) Define a minimally active dose (MAD), pharmacologically active dose (PAD), and maximum tolerated dose (MTD) of NC525 in subjects with advanced myeloid neoplasms

2.1.2. Secondary Objectives

1) To evaluate the clinical benefit of NC525
2) To evaluate the time to achieve an objective response (OR)
3) To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of NC525

2.1.3. Exploratory Objectives

1) To assess the immunogenicity of NC525
2) To explore biomarkers that may predict the pharmacologic activity of NC525

2.2. STUDY ENDPOINTS

2.2.1. Primary Endpoints

1) Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs). **Note:** Toxicity grading per NCI CTCAE v5.0
2) The recommended Phase 2 dose (RP2D) of NC525 in subjects with advanced myeloid neoplasms.
3) The MAD, PAD, and MTD of NC525 will be defined in subjects with advanced myeloid neoplasms.

2.2.2. Secondary Endpoints

1) Assessment of anti-leukemia activity/efficacy will be used to evaluate the clinical benefit of NC525, including:
    a. Objective Response (OR)
        - CR, CRi, or CRh and MLFS
    b. Event-free survival (EFS), and
    c. Overall survival (OS)
2) Assessment of time to achieve response, defined as CR, CRi, or CRh

a. To evaluate the time to achieve an objective response from Cycle 1 Day 1 to day remission is achieved as defined per protocol

3) Assessment of PK of NC525 concentration(s) in serum, as well as assessment of the PK/PD profile

2.2.3. Exploratory Endpoints

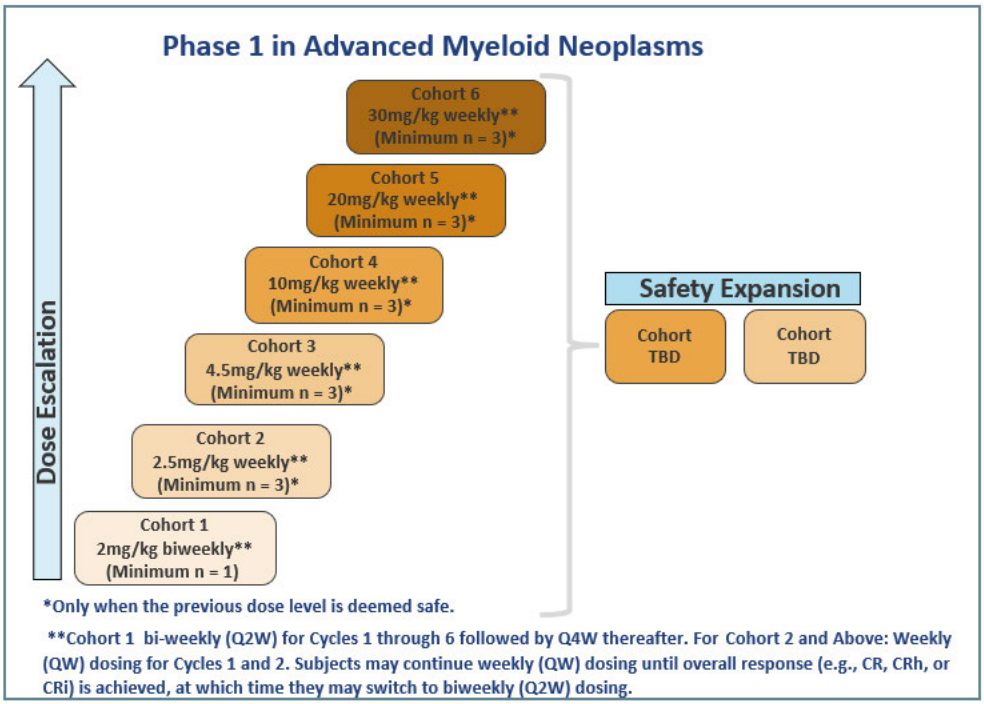
1) Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC525, will be determined
2) Biomarker effects of NC525 in peripheral blood and bone marrow will be assessed, including but not limited to the following:
    a. Percentage and/or expression level of LAIR-1 blast cells and/or Leukemic Stem Cells (LSC) or Hematopoietic Stem Cells (HSC)
    b. Any relation to response (clearing of blast cells to achieving CR)
    c. Serum markers of inflammation or immune modulation (cytokine & chemokine levels)

3. STUDY DESIGN

3.1. Description of the Study

This is an open-label, non-randomized, Phase 1 study to determine the safety and tolerability of NC525. This study will also assess the clinical benefit in subjects with advanced myeloid neoplasms. The study includes a dose escalation phase to determine MTD followed by expansion cohorts to further evaluate the safety and tolerability of the MTD (Figure 1).

Figure 1: Phase 1 Study Design



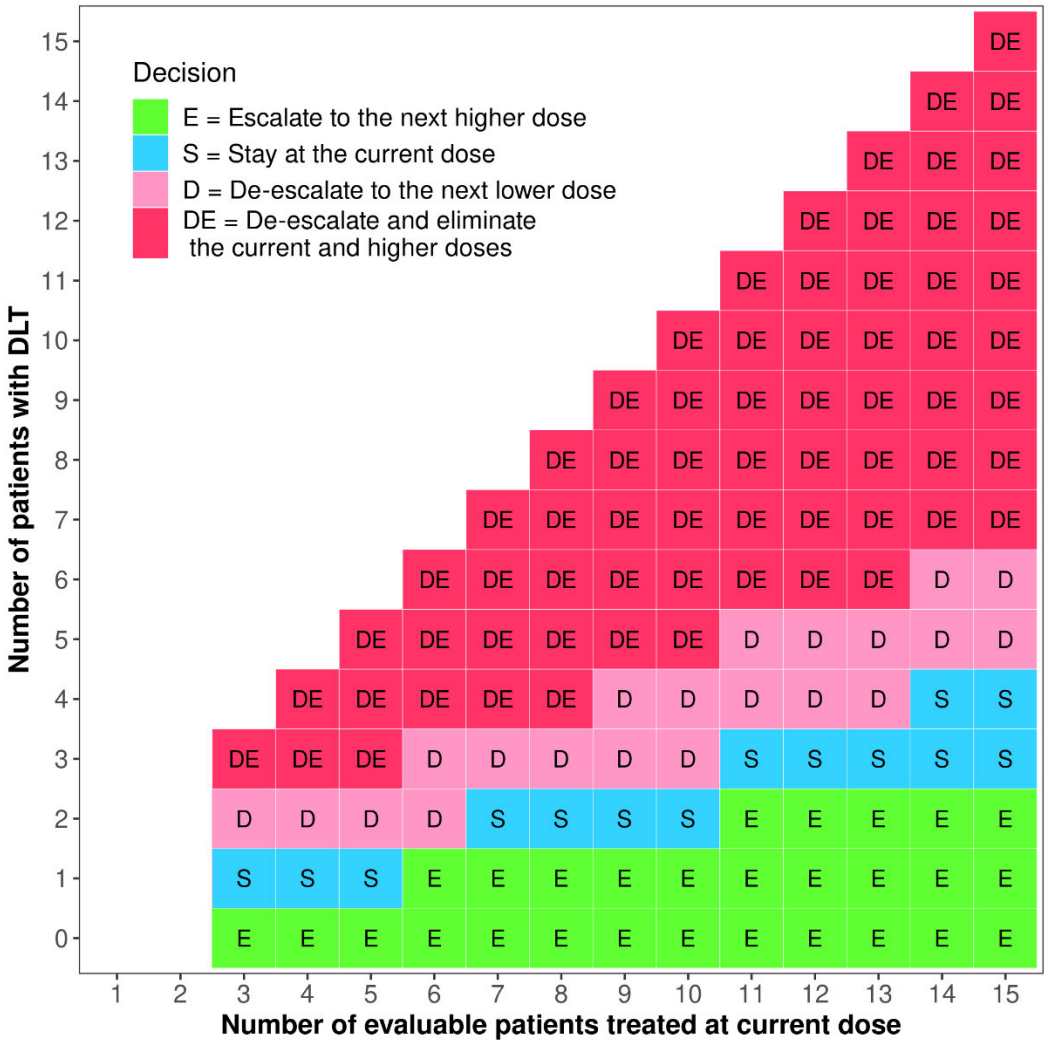
The safety and tolerability of NC525 will be evaluated by escalating dose levels of NC525. In addition, the minimally active dose (MAD), pharmacologically active dose (PAD), and maximum tolerated dose (MTD), of NC525 will be determined.

The PAD will be defined as a dose that provides a maximal biologic effect, such as achieving a complete remission (CR) and other variants of complete remission (CRh, CRi), and/or the MTD of NC525.

Once the biologically-effective dose(s) deemed to be safe have been identified, the safety and tolerability will be further assessed through expansion of two dose levels to determine an optimal Recommended Phase 2 Dose (RP2D) and administration schedule of NC525.

A Bayesian Optimal Interval (BOIN) design (Figure 2) with conventional 3+3 escalation rule fully nested for Phase I clinical trials (Liu S, Yuan Y, 2015) with a target dose-limiting toxicity (DLT) rate of approximately 25% will be applied for dose escalation and confirmation to determine a recommended Phase 2 dose (RP2D) for NC525.

Figure 2: Dose Finding Rules Per BOIN



3.2. Study Phase and Cohorts

3.2.1. Phase 1 Design

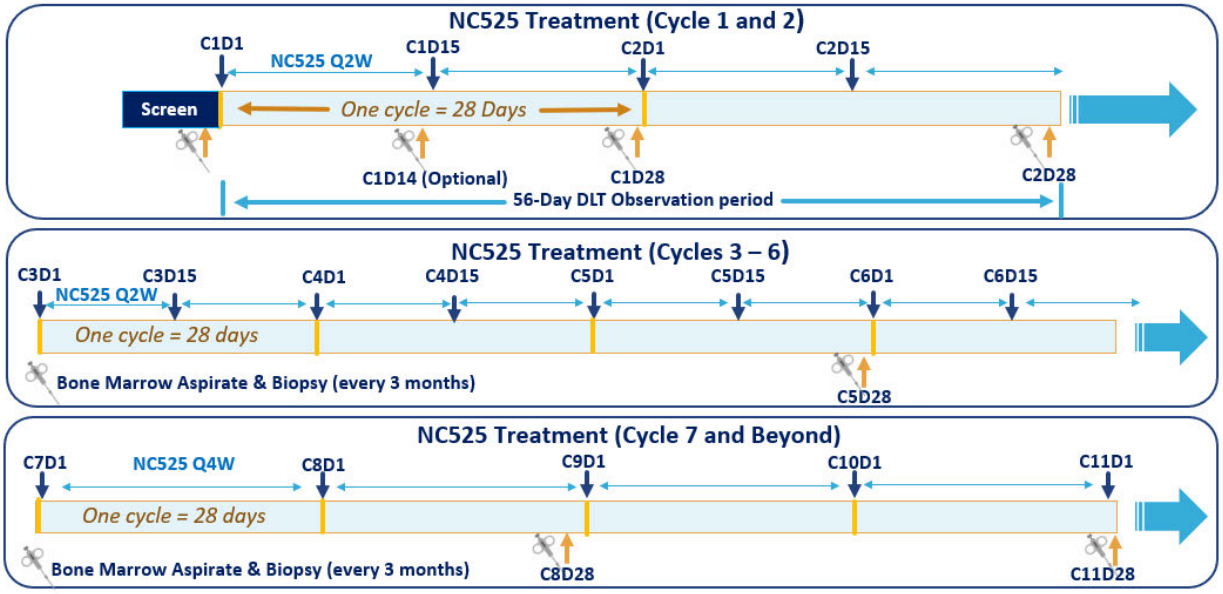
A BOIN design will be utilized to determine the MTD of NC525, where a minimum of 3 evaluable subjects will be enrolled at each level from Cohort 2 onwards. In the case of the starting dose level (2mg/kg), a minimum of 1 evaluable subject may be enrolled (in the absence of severe toxicity) prior to determining escalation to the next dose level given the dose is an approximation of the minimally active dose (PD30).

All dose escalation decisions will be based on the occurrence of DLTs at a given dose during the first 56-day period (i.e., first 2 cycles), also referred to as the DLT observation period (Figure 3). Dose escalation decisions will be made jointly by the Clinical Study Team comprised of the

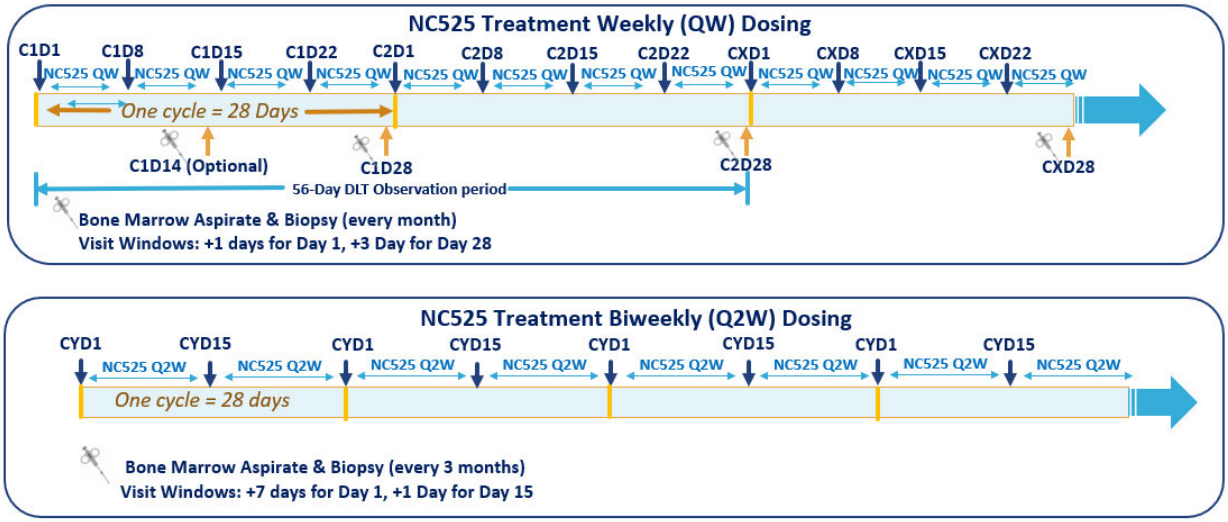
Sponsor Medical Monitor, CRO Medical Monitor and Investigators once the minimum number of evaluable subjects (n=3) have completed the DLT observation period.

Figure 3: Phase 1 Study Schema

a. Cohort 1



b. Cohort 2 and Above



A subject is considered evaluable if they have received at least four doses of NC525 and completed the 56-day DLT observation period or discontinued earlier due to an adverse event. Only one subject will be dosed on the first day of dosing for each cohort (additional subjects can begin in ≥ 48 hours). If there are multiple subjects in the screening process at the time the third subject within a cohort begins treatment, additional subjects may be enrolled with approval of the Sponsor using the BOIN design and based on the number of subjects evaluable at the current dose level.

The Escalation/De-escalation Rules per BOIN (Table 1) can be used to help inform decisions during the safety review meetings. Dosing decisions include escalate to the next higher dose, stay at the current dose, de-escalate to the next lower dose, or eliminate the dose level (i.e., unacceptably toxic dose). Dose escalation and de-escalation will be based on the cohort size of 3. That is, no dose escalation will be made before 3 patients are treated at the current dose, except the first dose where the accelerated titration may be performed and a minimum of 1 subject may be enrolled.

To reference the dose finding rules, one can use the number of evaluable subjects in a cohort that have been treated to determine the appropriate action based on the number of subjects who have experienced a DLT as indicated by the column. For example, at a given dose level, if 6 subjects have been enrolled but only 5 evaluable subjects have passed the 56-day DLT observation period, a decision could be made to escalate to the next dose cohort as long as there is ≤ 1 DLT in any of the 5 subjects.

Table 1: Dose escalation/de-escalation rule for the BOIN Design

Escalation/De-escalation Rules													
Action**	Number of evaluable patients treated*												
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Escalate if number of DLT ≤	0	0	0	1	1	1	1	1	2	2	2	2	2
Stay at current dose if number of DLT is equal to	1	1	1	NA	2	2	2	2	3	3	3	3, 4	3, 4
De-Escalate if the number of DLT ≥	2	2	2	2	3	3	3	3	4	4	4	5	5
Eliminate if number of DLT ≥	3	3	3	4	4	4	5	5	6	6	6	7	7

Note. "# of DLT" is the number of subjects with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of subjects.

*A subject is considered evaluable if they have received at least four doses of NC525 and completed the 56-day DLT observation period or discontinued earlier due to an adverse event.

**If de-escalation rule is met at Dose Level 1, alternative dose levels or administration schedules may be considered pending safety review and emerging data.

In addition to the BOIN dose finding rules, decisions to escalate to the next dose will be based on all available PK, PD, efficacy, safety, and tolerability data for the prior cohort(s). Efficacy measures consist of MLFS, CR, CRh, CRi and hematological recovery. Since NC525 targets and effectively kills leukemic blasts and LSC, PD marker comprises clearance of blasts from the marrow and peripheral blood. Further PD marker such as expression of LAIR-1 on blast cells to correlate with response will be assessed.

Two dose levels will be expanded to determine an optimal Recommended Phase 2 Dose (RP2D) and administration schedule of NC525. After Dose Escalation has been completed, safety

expansion up to 14 subjects per dose (including subjects treated at that dose level in the dose escalation phase) will be performed.

The doses for safety expansion are required to be no higher than the MTD and show sufficient PK/PD and anti-leukemic activities. The RP2D will be chosen based on an overall assessment of DLTs, safety profile, subject tolerance, biological activities and clinical efficacy signals collected at all different doses tested. The RP2D is required to be no higher than the MTD. A Bayesian toxicity monitoring rule will be used to ensure safety during safety expansion. Refer to Section 10.2.2 for details.

3.2.2. Dose Levels and Cohorts

The Dose Escalation part of the study will begin the following planned dose levels and cohorts:

- **Dose Level 1**: 2 mg/kg biweekly**
- **Dose Level 2**: 2.5 mg/kg* weekly**
- **Dose Level 3**: 4.5 mg/kg weekly**
- **Dose Level 4**: 10 mg/kg weekly**
- **Dose Level 5**: 20 mg/kg weekly**
- **Dose Level 6**: 30 mg/kg weekly**

** Cohort 1: Biweekly (Q2W) for Cycles 1 through 6 followed by every 4 weeks (Q4W) thereafter. Cohort 2 and above: Weekly (QW) dosing for Cycles 1 and 2. Subjects may continue QW dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to Q2W dosing.

The planned dose levels for Dose Escalation include a maximum dose increment of less than a half-log (233%) between each dose level. Using the Escalation/De-escalation Rules governed by the BOIN design, if criteria is met allowing dose escalation, the subsequent dose level will first be evaluated against the Dose Increment Modification Rules For Dose Escalation (Table 2) taking into consideration the number of adverse events (Grade ≥ 2) and dose limiting toxicities which occurred at the current dose level prior to selecting the next dose.

In the event a dose increment modification is indicated during the Dose Escalation phase of the study, an ad-hoc safety meeting will occur with the Clinical Study Team to review the adverse event(s) against the qualifying criteria before any dose modifications are made.

All Adverse Events (excluding AEs unequivocally due to the underlying disease or an extraneous cause) occurring during the DLT Observation Period will be evaluated against the Dose Increment Modification rules, as follows:

- Limit the maximum dose increment to 100% if patients of a given cohort experience <u>one</u> Grade ≥ 2 AE (except for AEs unequivocally due to the underlying disease or an extraneous cause) during the DLT period.
    - ***Example:*** *If one ≥ Grade 2 AE occurs in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 100% (4mg/kg) instead of the originally planned dose of 4.5mg/kg.*

- Limit the maximum dose increment to 50% if patients of a given cohort experience two or more Grade ≥ 2 AEs (except for AEs unequivocally due to the underlying disease or an extraneous cause) during the DLT period.
    - ***Example:*** *If two or more ≥ Grade 2 AE occurs in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 50% (3mg/kg) instead of the originally planned dose of 4.5mg/kg.*

- Limit the maximum dose increment to 50% if patients of a given cohort experience one DLT during the DLT period.
    - ***Example:*** *If one DLT occurs in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 50% (3mg/kg) instead of the originally planned dose of 4.5mg/kg.*

- Limit the maximum dose increment to 30% if patients of a given cohort experience two DLTs during the DLT period.
    - ***Example:*** *If two DLTs occur in Dose Cohort 1 (2mg/kg), the subsequent dose level will be increased by 30% (2.6mg/kg) instead of the originally planned dose of 4.5mg/kg.*

Table 2: Dose Increment Modification Rules for Dose Escalation

<table>
<tr><th rowspan="2">Dose Cohort</th><th rowspan="2">Planned Dose (mg/kg)</th><th rowspan="2">Frequency*</th><th colspan="5">Dose Increment Modification During DLT Observation Period</th></tr>
<tr><th>If No DLT and/or no Grade ≥ 2 AE[a] in a given cohort</th><th>If one Grade ≥ 2 AE[a] in a given cohort</th><th>If two or more Grade ≥ 2 AEs[a] in a given cohort</th><th>If One DLT in a given cohort</th><th>If 2 DLTs in a given cohort</th></tr>
<tr><td>1</td><td>2</td><td>Q2W</td><td rowspan="3">Dose increment as planned</td><td rowspan="3">Maximum dose increment to 100%</td><td colspan="2" rowspan="5">Maximum dose increment to 50%</td><td rowspan="6">Maximum dose increment to 30%</td></tr>
<tr><td>2</td><td>2.5</td><td>QW</td></tr>
<tr><td>3</td><td>4.5</td><td>QW</td></tr>
<tr><td>4</td><td>10</td><td>QW</td><td colspan="2">Dose increment as planned</td></tr>
<tr><td>5</td><td>20</td><td>QW</td><td colspan="2">Dose increment as planned</td></tr>
<tr><td>6</td><td>30</td><td>QW</td><td colspan="2">Dose increment as planned</td><td colspan="2">Dose increment as planned</td></tr>
</table>

a Adverse events (except for AEs unequivocally due to the underlying disease or an extraneous cause) occurring during the DLT Observation Period will be evaluated against the Dose Increment Modification rule.

*Cohort 1: Biweekly (Q2W) for Cycles 1 through 6 followed by every 4 weeks (Q4W) thereafter. Cohort 2 and above: QW dosing for Cycles 1 and 2. Subjects may continue QW dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to Q2W dosing.

3.3. Measures Taken to Avoid Bias

This is an open-label study; no formal comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

3.4. Number of Subjects

3.4.1. Planned Number of Subjects

Approximately 63 evaluable subjects may be enrolled in this study.

Phase 1 Dose Escalation – Up to 30 evaluable subjects.

Phase 1 Safety Expansion – Up to an additional 33 evaluable subjects may be enrolled.

3.4.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- If a subject withdraws from treatment before the completion of the DLT period for any reason other than a DLT (e.g., subject is not evaluable for DLTs)
- Subject does not meet the eligibility requirements of the study (accidental enrollment)

3.5. Duration of Treatment and Participation

After signing the informed consent form (ICF), screening assessments may be completed over a period of approximately 21 days. Subjects will continue for up to 2 years of treatment or until progressive disease, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons requiring cessation of treatment.

3.6. Overall Study Duration

The study begins when the first subject signs the ICF. Subjects may be eligible to receive study treatment for up to 2 years or until the criteria for discontinuation of treatment are met (whichever comes first).

The end of the study may be declared when no more than 5 subjects remain on study treatment for at least 6 months, at which point a database lock of the study may occur to allow for analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per standard of care until withdrawal criteria is met (Section 5.10). The investigator will be expected to monitor for and report any serious AEs (SAEs), ECI, overdoses, and pregnancies, as detailed in Sections 9.1, 9.1.3, and 9.33. The remaining subjects will be considered on study until a discontinuation criterion is met and written notification is provided to the sponsor.

3.7. Continued Access

Subjects who are still on study intervention at the time of study completion/termination may continue to receive study intervention if they are experiencing clinical benefit after one year. The continued access to study intervention will end when a criterion for discontinuation is met.

3.8. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The IRB must be notified in writing of the study's completion

or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain one copy for the site study regulatory file. The sponsor may terminate the study electively, if required by regulatory decision or upon review of emerging data. If the study is terminated prematurely, then the sponsor or designee will notify the investigators, the IRBs and regulatory bodies of the decision and reason for termination of the study.

4. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Subject Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1) The subject is willing to provide written informed consent for the trial.
2) Be ≥ 18 years of age on the day of signing informed consent.
3) Subject has one of the following Myeloid Neoplasms determined by pathology review at the treating institution:
   - Relapsed or Refractory AML,

     Note: Active, relapsed, or refractory AML is defined as any one of the following:
     - Primary induction failure, or (PIF) after 2 or more cycles of therapy,
     - First early relapse after a remission duration of fewer than 6 months,
     - Relapse refractory to salvage combination chemotherapy second or subsequent relapse, or
     - Relapsed or refractory AML with at least 5% blasts by bone marrow biopsy or aspirate, or at least 1% blasts in peripheral blood
   - Relapsed or Refractory Myelodysplastic syndrome (MDS) after prior hypomethylating agents

     Note: Subject must have sub-type MDS-EB2 with 10-19% blasts by bone marrow biopsy or aspirate.
   - Relapsed or Refractory Chronic myelomonocytic leukemia (CMML) with progressive disease or lack of response to hypomethylating agents
4) A male subject must agree to use approved contraception (based on institutional guidelines) and refrain from sperm donation or expecting to father a child, from Screening through the treatment period and for at least 90 days after the last dose of study treatment.
5) A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
   a) Not a woman of childbearing potential (WOCBP)
   b) A WOCBP agrees to follow approved contraceptive guidance (based on institutional guidelines) from Screening through the treatment period and for at least 90 days after the last dose of study treatment.
6) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
7) Life expectancy greater than or equal to 12 weeks as judged by the Investigator.
8) Have adequate organ function as defined in the following table (Table 3)

Table 3: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematology	
Peripheral white blood cell (WBC)	≤ 25,000/μL[1]
Renal	
Measured or calculated[2] creatinine clearance	Creatinine clearance > 60 mL/min
Hepatic	
Total bilirubin	<1.5 × ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 × ULN. **Note:** Subjects with documented Gilbert's syndrome with elevated baseline total bilirubin ≤ 3.0 mg/dL or indirect hyperbilirubinemia suspected to be result of hemolysis may be enrolled.
AST (SGOT) and ALT (SGPT)	≤ 3.0 × ULN

ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[1] Hydroxyurea or cytarabine therapy is allowed to reduce white blood cells to meet this inclusion criterion. White blood cells should be determined ≥ 24 hours after the last leukoreduction therapy administration. Final leukoreduction therapy administration should not be administered ≤ 3 days prior to the first dose of NC525 without medical monitor approval.

[2] Creatinine clearance (CrCl) should be calculated per institutional standard. GFR can also be used in place of creatinine or CrCl.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Note: Screening labs must be collected within 7 days prior to the start of study treatment.

4.2. Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria apply:

1) Has a diagnosis of acute promyelocytic leukemia (M3, APL), accelerated phase or blast crisis of chronic myeloid leukemia.
2) History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
3) Subjects with active Central Nervous System (CNS) involvement (such as leukemic infiltration, blast in the spinal fluid, or subjects with extramedullary disease).
4) A WOCBP who has a positive pregnancy test (within 72 hours) prior to treatment.
5) History or evidence of any other clinically significant disorder, condition or disease (e.g., symptomatic congestive heart failure, unstable angina pectoris, symptomatic myocardial infection, uncontrolled cardiac arrhythmia, pericardial disease or heart failure New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase subjects' risk for toxicity and in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
6) Chronic respiratory disease or any other medical condition that requires continuous oxygen that in the opinion of the Investigator, would adversely affect his/her participation in this study.
7) Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention.

   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
8) Is currently participating in or has participated in a study of the following prior to the first dose of study treatment:
   a. An investigational biologic or an investigational device within 4 weeks or 5 half-lives (whichever is longer);
   b. An investigational oral agent within 2 weeks or 5 half-lives (whichever is shorter).

   Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as the specified washout period has been completed.
9) Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior chemotherapy, targeted therapies, immunotherapy and radiation therapy) and/or complications from prior interventions before starting therapy.

   Note: Subjects with stable chronic conditions (≤ Grade 2) not expected to resolve (such as neuropathy and alopecia) are exceptions and may still enroll.

10) Has previously had an allogeneic solid organ transplant.

11) Autologous HSCT within 6 weeks before the start of study treatment.

12) Allogeneic HSCT within 6 months before the start of study treatment.

13) Any active acute or chronic graft-versus-host disease (GvHD), Grade 2-4, or active chronic GvHD requiring systemic treatment.

14) Any systemic therapy (e.g. calcineurin inhibitors (CNI), steroids, etc.) against GvHD within 4 weeks before the start of study treatment.

15) Any Grade ≥ 2 persistent non-hematological toxicity related to allogeneic transplant, such as those requiring systemic immunosuppressive therapy.

16) Previous CAR-T therapy.

17) Known concurrent malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry after treatment with curative intent.

    Note: Cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year are not considered exclusionary.

18) Has severe hypersensitivity (≥ Grade 3), known allergy or reaction to Immunoglobulins or NC525, and/or any of their excipients.

19) Uncontrolled systemic fungal, bacterial, viral, or other infection despite appropriate anti-infection treatment at the time of eligibility confirmation.

20) Has a known history of HIV infection. **Note**: No HIV testing is required unless mandated by the local health authority.

21) Has a known active chronic hepatitis B infection or chronic hepatitis C infection with the exception of those with an undetectable viral load within 3 months.

22) Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate, in the opinion of the treating investigator.

23) Has a known psychiatric or substance abuse disorder that would interfere with the subject’s ability to cooperate with the requirements of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

All eligible subjects, after signing the ICF, will be allocated by non-random assignment, and will receive a unique subject number with the first 4 digits serving as the site number.

Dose level and cohort assignment will occur at time of subject enrollment and as indicated by the sponsor or designee.

All subjects will be assigned to a cohort to receive NC525; there is no placebo.

5.1.2. Randomization and Blinding

This is an open-label nonrandomized study; therefore, randomization and blinding do not apply.

5.2. Description and Administration

5.2.1. NC525 Description

NC525 is in frozen liquid form formulated for IV infusion. NC525 is formulated at a nominal concentration of 60 mg/mL in 20 mM Histidine, 8% (w/w) sucrose, 0.03% (w/w) Polysorbate 80 pH 5.5. Additional information can be found in the NC525 IB.

5.2.2. Study Drug Administration

The subject dose (in mg/kg) is determined by cohort enrollment. Dosing will be based on subject's actual weight (or ideal body weight if considered obese) in kilograms. The site should determine and evaluate obesity based on institutional guidelines.

NC525 will be prepared by adding the drug product directly to a bag containing 0.9% sodium chloride injection USP (normal saline) and delivered through an IV administration set. Final infusion concentration must be at or above 0.4 mg/mL and no more than 20 mg/mL. (Refer to Appendix 7).

The use of 0.2 μm in-line filter is required for study drug administration.

Storage of study drug after preparation is limited to room temperature. Total in-use storage time from the dilution of NC525 in the dilution bag/container to the completion of the study drug infusion should not exceed 4 hours at room temperature. If the in-use storage time exceeds these limits, a new dose must be prepared from new vials.

NC525 must be administered by qualified personnel via IV infusion over a minimum of 30 minutes (subject to change depending on subject's assigned dose level). See Appendix 7 for further infusion instructions. The minimum infusion rate must be at least 6 ml/hour and not more than 1600 mg/hour. The NC525 Pharmacy Manual contains more specific instructions for the preparation and administration of NC525.

5.3. Supply Packaging and Labeling

Study drug will be packaged as open-labeled supplies, each vial will be labeled and placed in a carton. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of NC525.

5.4. Storage

NC525 must be stored in a -20°C freezer, protected from light, in a secure, controlled-access location. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Study drug may not be used for any purpose other than that stated in the protocol. The NC525 Pharmacy Manual contains additional information regarding storage of study drug.

5.5. Accountability

The investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, usage, and return or destruction of study drug in accordance with the protocol and any applicable laws and regulations.

Detailed information such as requirements for accountability can be located within the NC525 pharmacy manual, which will be provided separately.

5.6. Treatment Compliance

Compliance with NC525 dosing will be calculated by the sponsor based on the drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

5.7. Reporting Product Complaints

Any defects with the investigational products must be reported immediately to NextCure by the site with further notification to the site monitor. During the investigation of the product complaint, all investigational products must be stored per instructions in pharmacy manual unless otherwise instructed.

NextCure contact information for reporting product complaints:

Email: ClinicalSupply@nextcure.com

Email Subject Line should include: "***NC525-01 Product Complaint***"

5.8. Dose Modifications

5.8.1. Criteria and Procedures for Modifications, Dose Interruptions and Adjustments of Study Treatments

Treatment with NC525 may be delayed allowing for resolution of toxicities. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study.

For Cohort 1, NC525 is given by Intravenous (IV) infusion every two weeks (on Days 1 and 15 of each cycle) for the first 6 cycles. For subjects who continue on treatment beyond Cycle 6, NC525 will be administered every 4 weeks (on Day 1 of each cycle only).

For Cohort 2 and above, there are four doses per cycle when following the weekly (QW) dosing schedule. Cycles begin with the first dose of each cycle and no sooner than 7 days from the last dose of the prior cycle. Subjects may continue weekly (QW) dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to biweekly (Q2W) dosing. For subjects who achieve overall response and switch to a biweekly (Q2W) dosing schedule, there are two doses per cycle, cycles begin with the first dose of each cycle and no sooner than 14 days from the last dose of the prior cycle. Patients will be taken off study therapy if there is greater than a 14-day delay in scheduled treatment.

Cycles must be administered in consecutive order, and a cycle is never skipped even in the event of a delayed dose.

Study Treatment may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 2 weeks or 14 days unless otherwise discussed with the Sponsor.

Individual decisions regarding dose interruptions should be made using appropriate clinical judgment in consultation with the medical monitor, considering relatedness of the AE to the study treatments and the subject 's underlying condition. The Sponsor should be notified if a delay in study treatment is anticipated or occurs.

If study treatment is interrupted, the reason for interruption is to be documented in the subject's study record.

5.8.2. Instructions for Dose Modifications for Adverse Events

Given that this is a FIH study, it is difficult to determine suspected adverse events however, based on established product class effects certain adverse events and their recommended management are detailed below. The following guidance may used in addition to institutional guidelines to manage dose modifications for such adverse events (Table 4).

Table 4: Dose Modifications for Adverse Events

AE Toxicity grade (CTCAE V5.0)	Action with NC525
Grade 3 Immune-related AE (e.g. pneumonitis, colitis, elevated LFTs (in absence of active disease), etc.)	Interrupt Treatment, Restart treatment at one dose level lower when the specific immune-related AE resolves to no more than Grade 1 in severity. If immune-related AE does not resolve in 14 days, or if the Grade 3 immune-related AE recurs, the subject must permanently discontinue.
Grade 4 Immune-related AE (e.g. pneumonitis, colitis, elevated LFTs (in absence of active disease), etc.)	Permanently Discontinue

AE Toxicity grade (CTCAE V5.0)	Action with NC525
Grade 3 or Grade 4 Tumor Lysis Syndrome (TLS)	Interrupt Treatment, Restart treatment at the same dose when the TLS is resolved to no more than Grade 1 in severity within 2 weeks or 14 days, *For Management of TLS, see Appendix 5*
Any Grade Infusion Reaction	See Table 5 for management of infusion reaction.
Differentiation Syndrome (DS)[a] (Grading based on reporting of individual symptoms)	Interrupt Treatment, Administer corticosteroids per standard of care. Restart treatment at the same dose level with the DS is resolved within 2 weeks or 14 days.
New Onset Grade 4 Neutrophil Count Decrease lasting > 1 week[b]	Interrupt Treatment, Restart treatment at the same dose when the ANC is ≥ 500/µL within 2 weeks or 14 days. If Grade 4 neutropenia recurs, interrupt again but restart at one dose level lower when the ANC is ≥ 500/µL within 2 weeks or 14 days.
New Onset Grade 4 Platelet Count Decrease lasting > 1 week[b]	Interrupt Treatment, Restart treatment at the same dose when the platelet count ≥ 25,000/µL within 2 weeks or 14 days. If Grade 4 thrombocytopenia recurs, interrupt again but restart at one dose level lower when the platelet count is ≥ 25,000/µL within 2 weeks or 14 days.
Any other non-hematological Grade 3 (other than TLS) adverse reaction	Interrupt Treatment, Restart treatment at the same dose if the adverse reaction resolved to no more than Grade 1 in severity within 2 weeks or 14 days. If the adverse reaction recurs at Grade 4, the subject must permanently discontinue. If the adverse reaction recurs a second time at Grade 3, interrupt again, and the subject must permanently discontinue.
Any other non-hematological Grade 4 (other than TLS) adverse reaction	Permanently Discontinue

a Differentiation Syndrome as determined per PI based on institutional guidelines and in the absence of active infection, infusion reaction, heart failure, etc., with any of the following potential signs and symptoms: unexplained fever, weight gain, peripheral edema, dyspnea with interstitial pulmonary infiltrates, pleural and/or pericardial effusion, hypotension, acute renal failure, with or without increasing total WBC.
b In the absence of active myeloid neoplasms.

Note: For subjects who have not recovered ANC ≥ 500/μL or platelet count ≥ 25,000/μL within 14 days of drug interruption, a repeat bone marrow biopsy and aspirate may be performed to rule out active myeloid neoplasms at the investigator discretion before resuming the next cycle of study treatment.

5.8.3. Prophylaxis and Monitoring for Tumor Lysis Syndrome (TLS)

Since NC525 has never been tested in humans, a potential risk for TLS in subjects with advanced myeloid neoplasms cannot be discounted, especially in those with elevated leukocyte count, circulating blasts, elevated pretreatment LDH levels, renal dysfunction, and dehydration. To mitigate the risk for TLS all subjects enrolled into the study will need TLS prophylaxis and monitoring. Prophylactic reductions of potassium, inorganic phosphorus or uric acid above normal range are recommended prior to beginning study treatment and continue based on the ongoing risk of TLS.

Below are the minimum requirements for TLS prophylaxis and monitoring for subjects enrolled into the study. All other prophylaxis and monitoring procedures for TLS will be implemented as per regional guidelines/institutional standards:

- Administration of uric acid reducing agent, adequate oral, and IV hydration while monitoring the fluid status of the subject beginning on Day -1 of Cycle 1.
- For Cycle 1 Day 1 all subjects will be admitted to the hospital for the first 48 hours after study treatment or until the investigator deems the subject safe for continued outpatient monitoring.
- Administration of uric acid reducing agent, adequate oral, and IV hydration while monitoring the fluid status of the subject beginning on Day -1 of Cycle 1.
- TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) within 24 hours prior to NC525 dosing on C1D1 and 6 – 8 hours post dose. TLS chemistry will also be drawn 24 hours and 48 hours post-dose on C1D1. TLS Chemistry tests should also be drawn within 24 hours pre-dose on C1D8, C1D15 and C1D22, and 24 hours post-dose and 48 hours post-dose on C1D15.
- Additional laboratory assessments may be performed, per investigator discretion if clinically indicated.
- Abnormal chemistry tests should be treated promptly.
- If a subject meets criteria for clinically significant laboratory or clinical TLS (see Appendix 4), no additional NC525 dose should be administered until resolution.

For continued dosing of NC525, monitor for evidence of TLS during treatment, and manage abnormalities of serum creatinine, uric acid, and electrolytes promptly. For subjects at higher risk (i.e., circulating blasts), more intensive measures should be considered.

5.8.4. Toxicity Management of Infusion-Reactions Related to NC525

Table 5 shows treatment guidelines for subjects who experience an infusion reaction associated with the administration of study drug. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Adverse events that may be manifestations of infusion reactions may include but are not limited to:

- Fever
- Chills/Rigors
- Flushing
- Nausea/Vomiting
- Bronchospasms
- Hypotension/Hypertension

To prevent infusion reactions from occurring all subjects must be premedicated prior to administration of NC525. Suggested premedication within 1.0 hour (± 30 minutes) prior to infusion of NC525 is detailed below, however subjects may be premedicated based on institutional guidelines:

- Diphenhydramine 25 – 50 mg po or IV (or equivalent dose of antihistamine)
- Acetaminophen 500 – 1000 mg po or IV (or equivalent dose of analgesic)
- Ranitidine 150mg po (or equivalent dose of H2 antagonist)
- Solu-Cortef 100mg IV (or equivalent corticosteroid)

Table 5: Infusion Reaction Dose Modification and Treatment Guidelines (NC525)

NCI CTCAE v5.0 Grade of Sign or Symptom of Infusion-Related Reaction	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • Acetaminophen • NSAIDs • Narcotics • Prophylactic medications indicated for ≤24 hrs	Subject may be premedicated 1.5 h our (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE v5.0 Grade of Sign or Symptom of Infusion-Related Reaction	Treatment	Premedication at Subsequent Dosing
	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Discontinue study treatment permanently for subjects who develop a Grade 2 or higher hypersensitivity reaction despite adequate premedication.**	
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • Acetaminophen • Oxygen • Corticosteroids • Epinephrine** • NSAIDs • Narcotics • Pressors • Ventilator Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further study drug treatment.	No subsequent dosing

Abbreviations: IV = intravenous; NSAID = nonsteroidal anti-inflammatory drugs; po = orally.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

The above table is the recommended guidance, however subjects should be managed per institutional guidelines.

5.9. Dose Limiting Toxicities (DLTs)

5.9.1. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose

During Dose Escalation, the evaluation period for DLTs will begin on Cycle 1 Day 1 and will continue up to 56 days. All DLTs will be assessed by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. A DLT will be defined as the occurrence of any toxicity in Table 6, except for events clearly associated with the underlying disease or an extraneous cause (e.g., car accident).

Individual subject dose reductions may be made based on events observed at any time during treatment with NC525; however, for the purposes of dose cohort escalation/de-escalation, and expanding a dose cohort, the decisions will be made based on events that are observed from the first day of study treatment through and including the 56-day DLT period. Alternative dose levels may subsequently be determined based on relevant toxicities that become evident after the 56-day DLT period.

Table 6: Definition of Dose-Limiting Toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

Nonhematologic toxicity

• Any grade 3 nausea, vomiting or diarrhea that requires TPN, tube feeding, or hospitalization is a DLT without exception
• Any other grade 3 adverse reaction (including laboratory abnormalities) lasting more than 72 hours, with the following exceptions:
  o Grade 3 fatigue lasting >3 days
• Any grade 4 nonhematological adverse reactions.
• Any Hy's law case defined as:
  o Combined elevations in serum ALT >3 times the upper limit of normal (ULN) and bilirubin >2 ULN in the absence of alkaline phosphatase (ALP) elevation (<2 ULN). **Note**: Abnormal liver function tests as indicated by the criteria above will be considered a DLT if no other reason can be found to explain the combination of increased liver markers such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Hematologic toxicity
• Any grade >3 ANC or PLTS lasting more than 7 days is a DLT in the absence of active leukemia. **Note**: Patients with active leukemia are not evaluable for a hematological DLT.
General
• Any infusion reaction that is not resolved within 24 hours. • Any adverse reaction that resulted in dose reduction or withdrawal. • Any fatal adverse reactions.

5.9.2. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators may employ any measures or concomitant medications, after discussion with the medical monitor (whenever possible), necessary to optimally treat the subject.

5.9.3. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks (e.g., 28 days). During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.10. Withdrawal/Discontinuation of Subjects from Study Treatment

5.10.1. Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be removed from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Discontinuation of study treatment does not represent withdrawal from the study. A subject may discontinue from treatment but agree to remain on-study, as long as the subject does not withdraw consent.

If a subject is withdrawn, then every reasonable effort should be made to determine the reason for withdrawal, and this information should be recorded in the electronic case report form (eCRF).

Subjects must be withdrawn from the trial for any of the following reasons:

- The subject is lost to follow-up
- Consent is withdrawn for study (does not agree to follow-up); no additional data collection should occur

Subjects must discontinue from the study treatment but can continue to be monitored for any of the following reasons:

- Consent is withdrawn for treatment (agrees to follow-up)
- The subject becomes pregnant
- Confirmed progressive disease (except if Sponsor approves treatment continuation)
- Unacceptable adverse experiences
- Investigator’s decision to withdraw subject
- Subjects proceed to stem cell transplantation
- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR, CRh, or CRi and have been treated for two years with NC525
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.8.
- The study is terminated by the IRB, regulatory authority, or Sponsor

Subjects who discontinue study treatment but agree to remain on-study should continue to be followed according to the applicable Post-Treatment Follow-up schedule. All subjects will be followed for overall survival (OS) until death, withdrawal of consent, or the end of the study.

5.10.2. Withdrawal Procedures

If the decision is made to permanently discontinue the study treatment, an end-of-treatment (EOT) visit should be conducted. The date on which the decision was made to discontinue study treatment and the reason for treatment discontinuation will be recorded in the eCRF.

If a subject discontinues study treatment, the site monitor and Sponsor must be notified.

5.11. Concomitant Therapy During Study Treatment

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Certain medications or vaccinations are specifically prohibited prior to and during the study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from study drug or vaccination may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study drug or vaccination schedule requires the agreement of the investigator, the sponsor, and the subject.

5.11.1. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the treatment period of this study:

- Antileukemic systemic chemotherapy or biological therapy
- Investigational agents other than NC525
- Live or live attenuated vaccines
- Hematopoietic growth factors (G-CSF, GM-CSF, ESA)
- Steroid therapy during study participation should be limited to a lower dose and short duration if medically indicated. Exceptions can be inhalational steroids for the treatment of asthma or COPD, topical steroids and for prevention and/or treatment of transfusion-related reactions.
- Receipt of calcineurin inhibitors (CNI) while participating in the study

If the investigator determines that a subject requires any of the aforementioned treatments for any reason, all study treatments of NC525 must be discontinued.

6. SCHEDULE OF STUDY PROCEDURES

Table 7: Schedule of Study Procedures

CYCLES 1 AND 2 (WEEKLY (QW) DOSING)

Trial Period	Protocol Section	Screening Phase	Treatment[b] (28- day cycles)												Disease Assessment	Post-Treatment		
			Cycles 1 & 2															
Visit Day		Screening	Day -1 (Cycle 1 Only)	Day 1	Day 2	Day 3	Day 4	Day 8	Optional Day 14 (Cycle 1 Only)	Day 15	Day 16	Day 17	Day 18	Day 22	Day 28 or at Suspected PD	End of Treatment (EOT)	30-Day Safety Follow-Up[bb]	Survival Follow-Up[cc]
Scheduling Window (Days)		~ 21 Days		+1 day (Cycle 2)				+1 day		+1 day				+1 day	± 3 days		± 2 weeks	Every 2 Months
ADMINISTRATIVE PROCEDURES																		
Informed consent[a]	0	X																
Eligibility (I/E) criteria	4	X																
Demographics	8.3.1	X																
Medical History[e]	8.3.1	X																
Cancer History and Diagnosis	8.3.2	X																
Prior/Concomitant Medications[f]	8.4	←	←	←	←	←	←	←	←	X	→	→	→	→	→	→	→	
Document PRBC and platelet transfusions	8.4	←	←	←	←	←	←	←	←	X	→	→	→	→	→	→	→	
Post-Treatment Cancer Therapy	8.5															X	X	X
Survival Status	7.5.2				←	←	←	←	←	←	X	→	→	→	→	→	→	

Trial Period		Screening Phase	Treatment[b] (28- day cycles)												Disease Assessment	Post-Treatment		
			Cycles 1 & 2															
Visit Day	Protocol Section	Screening	Day -1 (Cycle 1 Only)	Day 1	Day 2	Day 3	Day 4	Day 8	Optional Day 14 (Cycle 1 Only)	Day 15	Day 16	Day 17	Day 18	Day 22	Day 28 or at Suspected PD	End of Treatment (EOT)	30-Day Safety Follow-Up[bb]	Survival Follow-Up[cc]
Scheduling Window (Days)		~ 21 Days		+1 day (Cycle 2)				+1 day		+1 day				+1 day	± 3 days		± 2 weeks	Every 2 Months
CLINICAL PROCEDURES																		
Administer NC525[c,s]	5.2.2			X				X		X				X				
Comprehensive PE[g]	8.6.2.1	X														X		
Targeted PE[h]	8.6.2.2			X				X		X				X	X			
TLS Prophylaxis and Monitoring[d]	5.8.3		X	X	X	X		X		X	X	X		X				
Vital signs and weight[i]	8.6.4	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Height	8.6.4	X																
ECOG performance	8.6.3	X		X				X		X				X				
12-lead ECG[j]	8.6.77	X																
AE assessment[k]	9.1		◄							X								►
LOCAL LABORATORY																		
Hematology with differential	Table 8	X[l]		X[m]	X	X		X	X	X[n]	X	X		X	X	X		
Comprehensive CMP	Table 8	X[l]		X[m]	X	X		X	X	X[n]	X	X		X	X	X		
Coagulation panel	Table 8	X[l]		X[m]				X		X[n]				X				
Urinalysis[o]	Table 8	X[l]																
Inflammatory Markers	Table 8	X[l]		X				X		X								
Hepatitis B and C	Table 8	X[l]																

Trial Period		Screening Phase	Treatment[b] (28- day cycles)												Disease Assessment	Post-Treatment		
			Cycles 1 & 2															
Visit Day	**Protocol Section**	**Screening**	**Day -1 (Cycle 1 Only)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Optional Day 14 (Cycle 1 Only)**	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 22**	**Day 28 or at Suspected PD**	**End of Treatment (EOT)**	**30-Day Safety Follow-Up[bb]**	**Survival Follow-Up[cc]**
Scheduling Window (Days)		**~ 21 Days**		**+1 day (Cycle 2)**				**+1 day**		**+1 day**				**+1 day**	**± 3 days**		**± 2 weeks**	**Every 2 Months**
Pregnancy Test	Table 8	X[q]		X[r]				X[r]		X[r]				X[r]		X[q]		
Bone Marrow Aspirate and Biopsy Local Disease Assessment (Flow Cytometry, Cytogenetics, Morphology)	Table 10	X[x]							X[y]						X[z]	X[dd]		X[ee]
CENTRAL LABORATORY																		
Pharmacokinetics (PK)[t]	Table 9			X	X	X	X	X		X	X	X	X	X				
Anti-Drug Antibodies (ADA)[u]	Table 9			X						X						X		
Cytokines[w]	Table 9			X				X		X				X				
Bone Marrow Immunophenotyping[v]	Table 10	X							X[y]						X			
Bone Marrow Aspirate and Biopsy (Smear, Touch Prep, or FFPE)[p]	Table 10	X							X[y]						X			

OTHER CYCLES (WEEKLY (QW) DOSING)

Trial Period	Protocol section	Treatment[b] (28- day cycles)							Post-Treatment		
		Cycle X (Weekly Dosing)						Disease Assessment	End of Treatment (EOT)	30-Day Safety Follow-Up[bb]	Survival Follow-Up[cc]
Visit Day		Day 1	Day 2 (Cycle 3 Only)	Day 3 (Cycle 3 Only)	Day 8	Day 15	Day 22	Every 28 Days or at suspected PD			
Scheduling Window (Days)		+ 7 days			+1 day	+1 day	+1 day	± 3 days		± 2 weeks	Every 2 Months
ADMINISTRATIVE PROCEDURES											
Prior/Concomitant Medications[f]	8.4	←				X		→			
PRBC and platelet transfusion documentation	8.4	←				X		→			
Post-Treatment Cancer Therapy	8.5								X	X	X
Survival Status	7.5.2	←				X		→			
CLINICAL PROCEDURES											
Administer NC525[c,s]	5.2.2	X			X	X	X				
Comprehensive PE[g]	8.6.2.1								X		
Targeted physical assessment[h]	8.6.2.2	X			X	X	X	X			
Vital signs and weight[i]	8.6.4	X	X	X	X	X	X	X	X		
ECOG performance	8.6.3	X			X	X	X				
12-lead ECG[j]	8.6.7										
AE assessment[k]	9.1	←				X		→			
LOCAL LABORATORY											
Hematology with differential	Table 8	X[n]	X	X	X[n]	X[n]	X[n]	X	X		
Comprehensive CMP	Table 8	X[n]	X	X	X[n]	X[n]	X[n]	X	X		
Coagulation panel	Table 8	X[n]			X[n]	X[n]	X[n]				
Inflammatory Markers	Table 8	X									
Pregnancy Test	Table 8	X[r]			X[r]	X[r]	X[r]		X[q]		
Bone Marrow Aspirate and Biopsy Local Disease	Table 10							X[z]	X[dd]		X[ee]

Trial Period	Protocol section	Treatment[b] (28- day cycles)							Post-Treatment		
		Cycle X (Weekly Dosing)						Disease Assessment	End of Treatment (EOT)	30-Day Safety Follow-Up[bb]	Survival Follow-Up[cc]
Visit Day		**Day 1**	**Day 2** (Cycle 3 Only)	**Day 3** (Cycle 3 Only)	**Day 8**	**Day 15**	**Day 22**	**Every 28 Days or at suspected PD**			
Scheduling Window (Days)		**+ 7 days**			**+1 day**	**+1 day**	**+1 day**	**± 3 days**		**± 2 weeks**	**Every 2 Months**
Assessment (Flow Cytometry, Cytogenetics, Morphology)											
CENTRAL LAB											
Pharmacokinetics (PK)[t]	Table 9	X[t]	X[t]	X[t]							
Anti-Drug Antibodies (ADA)[u]	Table 9	X[u]							X[u]		
Cytokines[w]	Table 9	X[w]									
Bone Marrow Immunophenotyping[v]	Table 10							X			
Bone Marrow Aspirate and Biopsy (Smear, Touch Prep, or FFPE)[p]	Table 10							X			

OTHER CYCLES (BI-WEEKLY (Q2W) DOSING)

Trial Period	Protocol section	Treatment[b] (28- day cycles)					Post-Treatment		
		Cycle Y (Biweekly Dosing)				Disease Assessment	End of Treatment (EOT)	30-Day Safety Follow-Up[bb]	Survival Follow-Up[cc]
Visit Day		Day 1	Day 2 (Cycle 3 Only)	Day 3 (Cycle 3 Only)	Day 15	Every 3 Cycles or at suspected PD			
Scheduling Window (Days)		+ 7 days			+1 day	± 7 days		± 2 weeks	Every 2 Months
ADMINISTRATIVE PROCEDURES									
Prior/Concomitant Medications[f]	8.4	← X →							
PRBC and platelet transfusion documentation	8.4	← X →							
Post-Treatment Cancer Therapy	8.5						X	X	X
Survival Status	7.5.2	← X →							
CLINICAL PROCEDURES									
Administer NC525[c,s]	5.2.2	X			X				
Comprehensive PE[g]	8.6.2.1						X		
Targeted physical assessment[h]	8.6.2.2	X			X	X			
Vital signs and weight[i]	8.6.4	X	X	X	X	X	X		
ECOG performance	8.6.3	X			X				
12-lead ECG[j]	8.6.7								
AE assessment[k]	9.1	← X →							
LOCAL LABORATORY									
Hematology with differential	Table 8	X[n]	X	X	X[n]	X	X		
Comprehensive CMP	Table 8	X[n]	X	X	X[n]	X	X		
Coagulation panel	Table 8	X[n]			X[n]				
Inflammatory Markers	Table 8	X							
Pregnancy Test	Table 8	X[r]			X[r]		X[q]		
Bone Marrow Aspirate and Biopsy Local Disease	Table 10					X[aa]	X[dd]		X[ee]

Trial Period	Protocol section	Treatment[b] (28- day cycles)					Post-Treatment		
		Cycle Y (Biweekly Dosing)				Disease Assessment	End of Treatment (EOT)	30-Day Safety Follow-Up[bb]	Survival Follow-Up[cc]
Visit Day		Day 1	Day 2 (Cycle 3 Only)	Day 3 (Cycle 3 Only)	Day 15	Every 3 Cycles or at suspected PD			
Scheduling Window (Days)		+ 7 days			+1 day	± 7 days		± 2 weeks	Every 2 Months
Assessment (Flow Cytometry, Cytogenetics, Morphology)									
CENTRAL LAB									
Pharmacokinetics (PK)[t]	Table 9	X[t]	X[t]	X[t]					
Anti-Drug Antibodies (ADA)[u]	Table 9	X[u]					X[u]		
Cytokines[w]	Table 9	X[w]							
Bone Marrow Immunophenotyping[v]	Table 10					X			
Bone Marrow Aspirate and Biopsy (Smear, Touch Prep, or FFPE)[p]	Table 10					X			

a. Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subjects signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 7 days prior to the first dose of trial treatment).
b. Treatment cycles will begin every 28 days (+ 1 day window for weekly dosing schedule and + 7-day visit window for biweekly dosing schedule).
c. NC525 will be administered every week during Cycles 1 and 2 on Day 1, Day 8, Day 15, and Day 22. Subjects, may continue weekly (QW) dosing until overall response is achieved (e.g., CR, CRi, CRh), at which time they may switch to biweekly (Q2W) dosing. For biweekly dosing, NC525 will be administered every two weeks on Days 1 and 15 of each cycle.
d. All subjects will be required to receive prophylaxis for TLS beginning on Day -1 of Cycle 1. Refer to Section 5.8.3 for more details on TLS Prophylaxis and APPENDIX 5– Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.
e. Medical history will include relevant medical or surgical treatment within the last 10 years considered to be clinically significant by the investigator.
f. Any prior medication received up to 21 days before the first dose of study drug should be recorded. All concomitant medications received up to 30 days after the last dose of study intervention should be recorded. Upon discontinuation of study treatment, only post-anticancer treatments and concomitant medications and procedures related to adverse events (including SAEs and ECIs) should be recorded. Please also refer to Sections 5.11.1 for details on prohibited and restricted medications.
g. Comprehensive Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. The comprehensive physical examination should include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes, as well as a brief neurological examination.
h. Targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. Notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.
i. During Cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose, at the end of infusion of study treatment (+10 minutes), and every 60 minutes ± 10 minutes thereafter for 2 hours or per PI discretion. At subsequent cycles, vital signs will be assessed pre-dose and at the end of infusion (+10 minutes) of study treatment. Additional vital signs may be collected per PI's discretion if indicated.
j. A standard 12-lead electrocardiogram (ECG) will be performed one time during screening using local standard procedures. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary at the discretion of PI.
k. All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before first study treatment must be reported by the investigator if they cause the subject to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, or a procedure. From the time of first study treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. SAEs and ECIs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new post-treatment cancer therapy, whichever is earlier. .
l. Laboratory tests for screening are to be performed within 7 days prior to the first dose of study treatment.
m. Local Laboratory samples on Cycle 1 Day 1 must be performed before the administration of any study treatment and should be reviewed by the investigator or designee and found to be acceptable prior to the administration of study drug.
n. On the day of study drug administration for all subsequent study treatments, pre-dose laboratory procedures can be conducted up to 72 hours before administration of study treatment. Local lab results should be reviewed by the investigator or qualified designee and found to be acceptable before treatment is initiated.
o. Urinalysis to be performed at Screening. Urine dipstick – if abnormal, perform microscopic urinalysis. Additional time points may be performed as clinically necessary at the discretion of PI.
p. Bone Marrow aspirate (smear, touch prep, or FFPE) will be sent to the Central Lab for retrospective central lab response analysis. Please refer to the Central Lab Manual for processing instructions.
q. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study drug. Serum pregnancy will also be performed at EOT.
r. For women of child-bearing potential only, urine pregnancy must be performed within 72 hours prior to study treatment and resulted before study drug administration. If positive, confirm results with serum pregnancy test.
s. During Cycle 1 Day 1, subjects will be required to stay at the study site for safety observation for 48 hours after administration of NC525 infusion. For all subsequent doses subjects will be required to be observed for 1 hour post NC525 infusion or per PI discretion. After Cycle 1 Day 1, NC525 may be administered in an outpatient setting per investigator discretion.
t. Refer to Table 9 for PK collection timepoints throughout the study.
u. Refer to Table 9 for ADA collection timepoints throughout the study.
v. Immunophenotyping (Bone Marrow) will be performed per Table 10. Please refer to the Central Lab Manual for instructions.
w. Refer to Table 9 for Cytokine collection timepoints throughout the study.

x. Historical bone marrow aspirates at screening will not be accepted, a bone marrow aspirate and biopsy must be performed for study entry to collect mandatory biomarker assessments.
y. Bone marrow aspirate and biopsy at Cycle 1 Day 14 is optional. If it is performed, immunophenotyping sample should also be collected.
z. Bone marrow aspirate and biopsy at the end of Cycle 1 must be performed prior to administration of Cycle 2. Bone marrow aspirate and biopsy at the end of Cycle 2 must be completed within 3 days prior to Cycle 3 Day 1. Local Disease Assessments must be reviewed by the investigator or qualified designee and found to be acceptable prior to the administration of study drug for Cycle 3. Bone marrow aspirate and biopsies should continue to be collected every 28 days during QW dosing schedule.
aa. All other subsequent bone marrow aspirate and biopsy collections during Q2W dosing, must be performed every 3 cycles (± 7 days) and upon concern for progressive disease.
bb. A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety assessment. The subject should be followed until a satisfactory clinical resolution of any adverse event is achieved. The Safety Follow-up may be performed by phone.
cc. Following the 30-day Safety Follow-up Visit, subjects should be followed approximately every 2 months to assess for survival status. For subjects who discontinue study drug for reasons other than disease progression, hematology and disease assessment data (per standard of care) will continue to be collected until PD or initiation of a new post-treatment cancer therapy. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
dd. Collect only if no bone marrow has been collected within last 6 – 8 weeks, or if relapse of disease has already been confirmed.
ee. If Bone Marrow is collected per SOC, results should be recorded during the survival follow-up period until the subject discontinues the study.

Table 8: Clinical Laboratory Test

Comprehensive CMP	Hematology		Coagulation	Hepatitis Screening
Sodium Potassium Chloride Bicarbonate Glucose Blood urea nitrogen (BUN) Creatinine Calcium Total protein Albumin Total bilirubin Indirect Bilirubin *Direct bilirubin (if total bilirubin is elevated above ULN)* Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Magnesium Phosphorus Lactate dehydrogenase (LDH) Uric Acid	**Complete blood count, including:** WBC Hemoglobin Hematocrit RBC MCV MCH MCHC Platelet count Neutrophils Lymphocytes Monocytes Eosinophils Basophils Blasts (if detected)	**Differential count including:** Neutrophils Lymphocytes Monocytes Eosinophils Basophils Blasts (if detected) Bands (if detected) Atypical lymphocytes (if detected) Nucleated RBC (if detected)	PT aPTT INR D-dimer (quantitative) Fibrinogen **Inflammatory Markers** C-reactive protein Ferritin **Urinalysis** Specific gravity Microscopic Exam[a] Glucose RBC Protein WBC	Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA* HCV antibody HCV-RNA* *Note: If HCV/HBV antibody or antigen tests are positive, reflex testing (HCV RNA and/or HBV DNA tests) should be performed to confirm results before assessing subjects' eligibility. **Pregnancy Testing** Female subjects of childbearing potential require a serum test at screening and EOT. Urine pregnancy tests will be performed on Day 1 of all other cycles. *Pregnancy tests (serum or urine) should be repeated if required by local regulations*

Abbreviations: aPTT = activated partial thromboplastin time; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
a. microscopic exam required if abnormal results

Table 9: Schedule of Pharmacokinetic (PK), Pharmacodynamic (PD) and Biomarker Sample Collection

Study Visit Assessment	PK	ADA	Serum Cytokine	Timing of Sample Collection
Cycle 1 Day 1	X	X	X	Pre-infusion
	X		X	Post-infusion (+10 min)
	X			4 h (± 30 min) post-infusion
Cycle 1 Day 2	X			Anytime (24hrs post infusion)*
Cycle 1 Day 3	X			Anytime (48hrs post infusion)*
Cycle 1 Day 4	X			Anytime (72hrs post infusion)*
Cycle 1 Day 8	X		X	Pre-infusion
Cycle 1 Day 15	X	X	X	Pre-infusion
	X		X	Post-infusion (+10 min)
	X			4 h (± 30 min) post-infusion
Cycle 1 Day 16	X			Anytime (24hrs post infusion)*
Cycle 1 Day 17	X			Anytime (48hrs post infusion)*
Cycle 1 Day 18	X			Anytime (72hrs post infusion)*
Cycle 1 Day 22	X		X	Pre-infusion
Cycle 2 Day 1	X	X	X	Pre-infusion
	X		X	Post-infusion (+10 min)
	X			4 h (± 30 min) post-infusion
Cycle 2 Day 2	X			Anytime (24hrs post infusion)*
Cycle 2 Day 3	X			Anytime (48hrs post infusion)*
Cycle 2 Day 4	X			Anytime (72hrs post infusion)*
Cycle 2 Day 8	X		X	Pre-infusion
Cycle 2 Day 15	X	X	X	Pre-infusion
	X		X	Post-infusion (+10 min)
	X			4 h (± 30 min) post-infusion
Cycle 2 Day 16	X			Anytime (24hrs post infusion)*
Cycle 2 Day 17	X			Anytime (48hrs post infusion)*
Cycle 2 Day 18	X			Anytime (72hrs post infusion)*
Cycle 2 Day 22	X		X	Pre-infusion
Cycle 3 Day 1	X	X	X	Pre-infusion
	X			Post-infusion (+10 min)
	X			4 h (± 30 min) post-infusion
Cycle 3 Day 2	X			Anytime (24hrs post infusion)*
Cycle 3 Day 3	X			Anytime (48hrs post infusion)*
Day 1 of Cycle 5, 7, 11	X	X	X	Pre-infusion
EOT		X		Anytime

Abbreviations: ADA = anti-drug antibody; h = hours; min = minutes; PK = pharmacokinetics; EOT = End of Treatment

*PK sample(s) is expected to be collected as close to the planned time as operationally feasible and the exact PK collection date and time should be recorded.

Table 10: Schedule of Bone Marrow Biopsies and Bone Marrow Immunophenotyping

Timing of Sample Collection	Bone Marrow Aspirate and Biopsy Local Disease Assessment (Flow Cytometry, Cytogenetics, Morphology)	Bone Marrow Immunophenotyping	Bone Marrow Aspirate and Biopsy (Smear, Touch Prep, or FFPE)**
Screening	X	X	X
Cycle 1 Day 14	X*	X*	X*
Day 28 or at suspected PD For QW Dosing Schedule	X	X	X
Every 3 Cycles Thereafter, and at suspected PD for Q2W Dosing Schedule	X	X	X

*Optional
** Sample should be split from the local bone marrow disease assessment.

7. STUDY VISIT SCHEDULE

7.1. Screening Period

Screening is the interval between signing the ICF and the day the subject is enrolled (treated). Screening should be completed over approximately 21 days. Informed consent must be obtained before performing any study-specific procedures that are not considered standard of care. However, procedures conducted as part of the subject 's routine clinical management obtained before signing of informed consent may be used for screening or baseline purposes with approval of the medical monitor, provided that the procedure meets the protocol-defined criteria. Assessments that are required to demonstrate eligibility may be performed over the course of one or more days during the screening process.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or administration of study drug. Tests with results that fail eligibility requirements may be repeated **once** during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process **1 time** if the investigator believes there has been a change in eligibility status (e.g., after recovery from an infection). Treatment should start as soon as possible after the date of enrollment.

7.2. Treatment Period

The treatment period begins on Day -1 prior to the first dose of study treatment through the point at which the investigator determines that the subject will be permanently discontinued from study treatment.

7.3. Treatment Schedule

For Cohort 1, NC525 is given by Intravenous (IV) infusion every two weeks (on Days 1 and 15 of each cycle) for the first 6 cycles. For subjects who continue on treatment beyond Cycle 6, NC525 will be administered every 4 weeks (on Day 1 of each cycle only).

For Cohort 2 and above, NC525 will be administered every week on Days 1, 8, 15 and 22 during Cycles 1 and 2. Subjects may continue weekly dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to biweekly dosing. For biweekly dosing, NC525 will be administered every two weeks on Days 1 and 15 of each cycle. Subjects who derive clinical benefit may continue to receive NC525 for a total of 2 years or until the criteria for discontinuation of treatment are met (whichever comes first). A detailed description of the dosing schedule is included below (Table 11):

Table 11: NC525 Dosing Schedule

a. Cohort 1

Dosing Schedule													
Frequency	**Q2W**												**Q4W**
Cycle	**1**		**2**		**3**		**4**		**5**		**6**		**7+**
Day	1	15	1	15	1	15	1	15	1	15	1	15	1

b. Cohort 2 and Above

Dosing Schedule						
Frequency	**Weekly (QW)***				**Biweekly (Q2W)**	
Window	+1 day				+7 days	+1 day
Day	1	8	15	22	1	15

* Subjects may continue QW dosing until overall response (e.g., CR, CRh, or CRi) is achieved, at which time they may switch to Q2W dosing.

Subjects who derive clinical benefit may continue to receive NC525 for a total of 2 years or until the criteria for discontinuation of treatment are met (whichever comes first). Each cycle will be 28-days in duration.

Note: *Subjects who achieve complete remission and are eligible for an allogeneic SCT may elect to undergo allogeneic SCT at the discretion of the PI at any time point.*

Alternate dose levels and administration schedules, including ramp-up to target dose, may also be explored depending on PK, pharmacodynamic (PD), biomarkers, safety results, and feedback from investigators.

7.3.1. Treatment Discontinuation

Subjects will continue until progressive disease (PD), initiation of a new post-treatment cancer therapy, unacceptable adverse events (AEs), intercurrent illness that prevents further treatment administration, Investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements.

7.4. End of Treatment Visit

When the subject permanently discontinues study treatment, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to participate in the Post-Treatment follow-up period.

7.5. Post-Treatment Follow-up

7.5.1. 30 Day Safety Follow-Up Visit

A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety assessment. If the subject has an AE which is ongoing at the time of the visit, the subject will be followed until a satisfactory clinical resolution of the adverse event is achieved. Safety Follow-up may be performed by phone.

If the subject refuses or is unable to attend the Safety Follow-Up Visit, this should be noted in the subject's source documentation.

7.5.2. Survival Follow-Up

Following the 30-Day Safety Follow-Up Visit, overall survival and post treatment information (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of treatment initiation and completion, etc.) will be collected via telephone follow-up approximately every 2 months until death, withdrawal of consent, or the end of the study, whichever occurs first.

For subjects who discontinue study drug for reasons other than disease progression, hematology, and disease assessment data (per standard of care) will continue to be collected until PD or initiation of a new post-treatment cancer therapy.

7.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

8. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled timepoints if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HBV, HCV), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the subject before conducting any study-specific procedures using an ICF approved by the IRB and/or other regulatory authorities (as required per local laws and regulations). The ICF should contain all elements required by ICH E6 and describe the nature, scope, and possible consequences of the study in a manner that the subject can understand. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

8.2. Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as subjects in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

8.3. Demography and Medical History

8.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Disease details will be recorded separately and not listed as medical history.

Please note that if the subject has lost at least 15 lbs. (6.8 kg.) over the three months prior to screening, “weight loss” should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

8.3.2. Disease Characteristics and Prior Anticancer Treatment History

A disease-targeted medical and medication history will be collected at screening. Details regarding the subject 's malignancy under study including but not limited to date of diagnosis and subtype, antecedent hematologic disorder histology, and prior treatments, and surgical procedures will be recorded.

8.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and procedures must be recorded in the eCRF, and any medication received, or procedure performed within 21 days before the first dose of study drug.

All concomitant medications administered during the study will be recorded on the eCRF, including all prescription, over the counter, vaccines, herbal supplements, and iv medications and fluids. Any addition, deletion, or change in the dose of these medications should also be recorded. Concomitant treatments and/or procedures that are required to manage a subject 's medical condition during the study will also be recorded in the eCRF.

Upon discontinuation of study treatment, only post-anticancer treatments and concomitant medications and procedures related to adverse events (including SAEs and ECIs) should be recorded.

8.5. Post-Treatment Cancer Therapy

The investigator or qualified designee will review all new post treatment cancer therapy initiated after the last dose of study drug, including all post treatment cancer therapies including stem cell transplantation, regimens, dates of treatment initiation and completion, etc. Once new anti-leukemic therapy has been initiated the subject will move into survival follow-up.

8.6. Clinical Assessments and Procedures

8.6.1. Adverse Event Monitoring

Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of new or worsening AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?". All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 9.1.

8.6.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

8.6.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes, as well as a brief neurological examination. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.6.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include

assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.6.3. Eastern Cooperative Oncology Group Performance Status

The investigator will assess Eastern Cooperative Oncology Group (ECOG) performance status at Screening, and on Days 1, 8, 15, and 22 during QW dosing. ECOG will also be performed at Days 1 and 15 during Q2W dosing. More information on assessing performance status using ECOG can be found in 03.

8.6.4. Height, Weight, and Vital Signs

Weight will be assessed at each study visit. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Height will be recorded at Screening only.

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse should be taken with the subject in the recumbent or semi recumbent position after 5 minutes of rest.

During Cycle 1, vital signs will be assessed pre-dose, at the end of infusion (+10 minutes), and every 60 minutes ± 10 minutes thereafter for 2 hours and for longer timepoints per PI discretion.

At subsequent cycles, vital signs will be assessed pre-dose and at the end of infusion (+10 minutes). Additional vital signs may be collected per PI's discretion if indicated.

8.6.5. Tumor Lysis Syndrome (TLS) Prophylaxis

All subjects will be required to receive prophylaxis for TLS beginning on Day -1 of Cycle 1. Refer to Section 5.8.3 for more details on TLS Prophylaxis and Monitoring.

8.6.6. Safety Observation

NC525 may be administered in an outpatient setting. However, for Cycle 1 Day 1 all subjects will be admitted to the hospital for the first 48 hours after study treatment or until the investigator deems the subject safe for continued outpatient monitoring.

During subsequent doses, subjects will be required to stay at the study site for safety observation for 1 hour post NC525 infusion or per PI discretion.

At the Investigators discretion, further treatment can be delivered in an inpatient setting for subjects with disease characteristics that, in the Investigators clinical judgment, put the subject at higher risk of complications (e.g., TLS).

8.6.7. 12-Lead Electrocardiogram

All 12-lead ECGs should be performed with the subject in a recumbent or semi recumbent position after 5 minutes of rest. A single 12-lead ECG will be performed at Screening. Additional ECGs should be performed per PI discretion if any clinically significant abnormal findings are noted or as indicated.

8.6.8. Local Safety Laboratory Assessments

A laboratory, local to the study site and subject, will perform all clinical laboratory assessments for safety (e.g., blood chemistries, hematology assessments, inflammatory markers, coagulation tests, and urinalysis). All local laboratory assessments should be performed using standard procedures on the days indicated in the Schedule of Study Procedures in Table 7. Additional information regarding the specific laboratory analytes required for each test are detailed in Table 8. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Laboratory tests for screening are to be performed within 7 days prior to the first dose of study treatment on Cycle 1 Day 1.

On Day 1 of all cycles, pre-dose laboratory procedures should be collected within 72 hours and results should be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of study treatment.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator may repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study, requires a subject to receive treatment, meets protocol specific criteria (see Section 5.9 regarding toxicity management) and/or the investigator considers clinically significant will be recorded as an adverse event.

8.6.9. Pregnancy Testing

A local laboratory serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study drug. Urine pregnancy tests will be performed locally as outlined in Table 8. If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, then the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

8.6.10. Hepatitis Screening Tests

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 8. **Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results.**

8.6.11. Central Laboratory Assessments

Sample collection, processing, storage, and shipment instructions for the Central Laboratory assessments will be provided in the laboratory manual.

8.7. Pharmacokinetic Assessments

PK and ADA samples should not be collected through the same line in which the study drug is infused. If a central line is used for study drug infusion, collect PK and ADA samples via peripheral blood draw to prevent sample contamination.

Pre-infusion is defined as within 24 hours before administration of any study treatment. Adjustments to the timing of blood sampling may be made based on emerging PK data. The exact date and time of each PK and ADA blood draw will be recorded in the eCRF. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

8.8. Biomarker and Correlative Assessments

Serum cytokine and biomarker samples will be collected at the visits outlined in the Schedule of Study Procedures. If a central line is used for study drug infusion, collect blood samples via peripheral blood draw to prevent sample contamination. Additional biomarker assessments that might be correlated with safety, response, or resistance to treatment beyond those listed (e.g., monitoring inflammatory markers, measuring specific cell populations, tumor markers, RNA profiles of specific cell populations, or measuring cell surface markers by flow cytometry, Western blot, mass spectroscopy, or immunoassay) may be evaluated at the discretion of the sponsor using excess translational biomarker or PK samples. All analyses will be conducted by NextCure or NextCure's designee. For information regarding handling/shipping of specimens, please refer to the Central Laboratory Manual for the study.

8.9. Bone Marrow Biopsies

8.9.1. Bone Marrow Biopsy Collection Requirements

Bone Marrow Biopsy samples are required for participation in the study. Mandatory biopsies will be collected as specified below:

Screening: Bone marrow aspirate and biopsy are required at screening to confirm diagnosis.

On-treatment: On-treatment bone marrow aspirate and biopsy are required on Cycle 1 Day 28 and at the end of Cycle 2. Cycle 1 Day 14 bone marrow aspirate and biopsy is optional per PI discretion. Bone marrow aspirates and biopsies will continue to be collected every 28 days during QW dosing.

All other subsequent bone marrow aspirate and biopsy collections during Q2W dosing must be performed every 3 cycles and upon concern for progressive disease.

At the End of Treatment (optional), The End of Treatment (EOT) bone marrow aspirate and biopsy may be obtained at the time that study treatment has been discontinued. (If no bone marrow collected within the last 6 – 8 weeks, or if relapse of disease has already been confirmed).

NOTE: Details and methods for obtaining, processing, and shipping bone marrow biopsy samples will be provided in the Central Laboratory Manual for the study.

8.9.2. Bone Marrow Aspirate and Biopsy for Disease Assessment

Historical bone marrow aspirates and biopsies at screening will not be accepted; a bone marrow aspirate and biopsy must be performed for study entry to collect mandatory biomarker assessments. The bone marrow aspirate and/or biopsy should be performed after all other eligibility criteria have been met. Bone marrow aspirates and/or biopsies performed as standard of care throughout the study should also be captured on the appropriate eCRF.

A sufficient bone marrow aspirate and bone marrow core biopsy must be collected for all subjects at each of the disease assessments for local pathology assessment, mandatory biomarker assessments and retrospective central lab response analysis.

9. SAFETY MONITORING AND REPORTING

9.1. Adverse Events (AEs)

9.1.1. Adverse Event Definition

For the purposes of this protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related, that occurs after a subject provides informed consent and through the follow-up period. Both nonserious and serious AEs (SAEs) will be monitored throughout the study.

A pre-treatment event (PTE) is one that occurs after the time of informed consent (e.g., during the screening process) but prior to study drug administration. PTEs directly related to a study test or procedure should be reported during the Screening period.

Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF.

Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (e.g., hematologic abnormality that requires transfusion), or require changes in the study drug(s).

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Hospitalization of a subject to allow for observation and management (e.g., IV hydration) for the purpose of TLS prophylaxis will not be captured as an SAE unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization is met.

9.1.2. Serious Adverse Event Definition

An SAE is defined as an event that meets at least 1 of the following criteria:

- **Death of Subject**
  - An event that results in the death of a subject.
- **Life-Threatening**
  - An event that, in the investigator's opinion, would have resulted in immediate fatality if the medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
- **Hospitalization or Prolongation of Hospitalization**
  - An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
- **Congenital Anomaly**
  - An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- **Persistent or Significant Disability/Incapacity**

  - An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
- **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome**
  - An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of the subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

Progressive disease is not considered a serious adverse event, unless symptoms and clinical manifestations of disease progression meet any of the SAE criteria noted above.

9.1.3. Events of Clinical Interest (ECI)

Since NC525 has never been used in clinical trials, selected non-serious and serious adverse events are listed below as Events of Clinical Interest (ECI) and must be reported to the Sponsor **within 24 hours of awareness** by the Investigator. Since NC525 is a humanized monoclonal antibody, infusion reactions may occur. Furthermore, treatment of advanced myeloid neoplasms may cause differentiation syndrome and tumor lysis syndrome. Therefore, ECI are listed as precautionary for safety of subjects participating in NC525 study.

For the time period beginning with initiation of study treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor.

Events of clinical interest for this trial include:

- Infusion Reaction
- Tumor Lysis Syndrome
- Differentiation Syndrome
- An adverse event meeting definition of a DLT as defined in Section 5.9.1.

9.1.4. Management of Myelosuppression Related to Disease

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in subjects with myeloid neoplasms. Subjects with baseline neutropenia might be particularly at high risk.

Anti-infective prophylaxis should be implemented per regional guidelines or institutional standards including appropriate prophylaxis for bacterial, viral, and fungal infections. Treatment of sepsis and other infections (e.g. viral, other infections) should be managed per institutional guidelines.

Red blood cell transfusion and platelet transfusion should be given per institutional guidelines. Erythropoietin-stimulating agent (ESA), Granulocyte Colony Stimulating Factor (G-CSF), and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) are not permitted.

9.1.5. Reporting of an Overdose

For NC525, a definitive "overdose" level is unknown at this time. For the purpose of this trial, an overdose of NC525 will be defined as a subject receiving a dose of NC525 in excess of that assigned to them at the time of enrollment unless the alternative dose level was otherwise authorized by the Sponsor prior to administration.

Any overdose of a study subject with NC525 with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor or its designee. If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

9.1.6. Reporting of AEs

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome.

The severity of AEs will be assessed using NCI CTCAE v5.0 Grades 1 through 5.

If an event is not classified by NCI CTCAE, the severity of the AE will be graded according to Table 12 to estimate the grade of severity.

Table 12: NCI CTCAE v5.0 Grading Scale

Grade	Clinical Characteristics
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.

Grade	Clinical Characteristics
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences: urgent intervention indicated.
Grade 5	Death

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (NCI CTCAE v5.0 Grade 1 to 5).
- Relationship to study drug: unrelated, unlikely related, possibly related, probably related, and definitely related. See Appendix 1.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with study drug.
- The event outcome (e.g., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per SAE definition provided in Section 9.1.2.

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy (e.g., procedure), this action should be recorded on the AE eCRF and the event should be correlated as the indication on the appropriate eCRFs as applicable.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (e.g., between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

9.1.7. Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before first study treatment must be reported by the investigator *if they cause the subject to be excluded from the study or are the result of a protocol-specified intervention*, including but not

limited to washout or discontinuation of usual therapy, diet, or a procedure. SAEs and ECIs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new post treatment cancer therapy, whichever is earlier.

All AEs from the time of first study treatment through 30 days following cessation of study treatment must be reported by the investigator.

All SAEs or ECIs, from the time of first study treatment through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new post-treatment cancer therapy, whichever is earlier must be reported by the investigator.

All pregnancies and exposure during breastfeeding, from the time of first study treatment through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new post-treatment cancer therapy must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be study drug related.

9.1.8. Reporting of SAEs or ECIs

Within 24 hours of identifying an SAE/ECI, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and submit it to the Sponsor or its designee. Instructions for SAE/ECI reporting will be provided by the CRO. The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor or delegate as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying the Sponsor or its designee of an SAE/ECI. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE/ECI also needs to be provided the Sponsor or its designee within 24 hours of learning of the new information.

9.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the AE eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (e.g., "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 9.1.2.

9.3. Pregnancy

If a subject inadvertently becomes pregnant while on study treatment with NC525 the subject will be immediately discontinued study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

When a pregnancy has been confirmed in a subject (or a male subject's partner) during maternal or paternal exposure to study drug within 90 days of the last dose of study treatment or 30 days if a new post treatment cancer therapy is initiated, the following procedures should be followed to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only).
- Consent must be obtained from female partners of male subjects.
- The investigator must complete and submit the Clinical Trial Pregnancy form to the sponsor or its designee within 24 hours of learning of the pregnancy.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result (female subjects only).

  If a negative serum test does not confirm the urine pregnancy test result, then:

  - The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine whether it is in the subject's best interest to resume study drug and continue participation in the study.
- The EOT visit evaluations must be performed (female subjects only).

Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy outcomes of spontaneous abortion missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the study treatment to any pregnancy outcome.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

9.4. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in the NC525 IB. Additional safety information collected between IB updates will be communicated to Investigators as it becomes available. Any important new safety information should be discussed with the subject during the study, as necessary, and provided to the IRB. If new significant risks are identified, they will be added to the ICF.

9.5. Procedures for Cohort Safety Review and Dose Escalation Meetings

Telephone conferences will be scheduled by the sponsor, or sponsor's delegate, with the Clinical Study Team to review cohort-specific data and overall safety data, make dose escalation/de-escalation decisions, evaluate dose increment modifications, agree on dose finding, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

10. STATISTICS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (SAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Tabular summaries will be presented by dose groups. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimal, and maximal values. All analyses, unless specified otherwise, will be based on as-treated population, which includes all subjects who receive any dose of NC525. Additional details of statistical analyses will be described in a supplemental SAP.

10.1. Statistical Analysis Overview

Key elements of the statistical analysis plan are summarized in Table 13.

Table 13: Key Elements of the Statistical Analysis Plan (SAP)

Element	Plan for analysis
Study Design Overview	This is an open-label, non-randomized, Phase 1 study to determine the safety and tolerability of NC525. This study will also assess the clinical benefit in subjects with advanced myeloid neoplasms.
Analysis Populations	Safety Analysis Set (SAS): The SAS will include all the subjects who receive any amount of NC525 and will be used for summaries and analyses of safety data. PK Analysis Set (PAS): The PAS will include all the subjects whose blood samples are collected for PK analysis and will be used for PK data summaries and analyses. Full Analysis Set (FAS): The FAS includes all subjects enrolled in the study who received at least one full dose of NC525. The FAS will be used for summaries and analyses of all data that are not safety or PK
Primary Endpoint(s)	1) Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs). Note: Toxicity grading per NCI CTCAE v5.0 2) The recommended Phase 2 dose (RP2D) of NC525 in subjects with advanced myeloid neoplasms. 3) The MAD, PAD, and MTD of NC525 will be defined in subjects with advanced myeloid neoplasms.

Secondary Endpoints	1) Assessment of anti-leukemia activity/efficacy will be used to evaluate the clinical benefit of NC525, including: a. Objective Response (OR) i. CR, CRi, or CRh and MLFS b. Event-free survival (EFS), and c. Overall survival (OS) 2) Assessment of time to achieve response, defined as CR, CRi, or CRh a. To evaluate the time to achieve an objective response from Cycle 1 Day 1 to day remission is achieved as defined per protocol 3) Assessment of PK of NC525 concentration(s) in serum, as well as assessment of the PK/PD profile
Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	Using the FAS, all the efficacy data will be summarized by dose level and cohort. The PK analyses will be based off the PAS, and PK time-concentration data will be summarized, listed, and plotted. PK parameters (AUC_{0-168}, $AUC_{0-\infty}$, Cmax, $t_{½}$, etc.) derived from time-concentration data will be summarized.
Treatment Assignment	This is an open-label study.
Statistical Methods for Safety Analyses	All the safety data in the SAS will be summarized and listed by dose level and cohort.
Interim Analyses	No formal interim analysis is planned. However, the safety, PK and efficacy data will be regularly reviewed and monitored for decisions involving the dose escalation and safety expansion parts of the study.
Multiplicity	Individual cohorts will be evaluated independently.
Sample Size and Power	The overall study sample size is approximately 63. Dose Escalation: The planned sample size is up to 30 subjects. Safety Expansion: The planned sample size is up to 33 subjects

Abbreviations: AE = adverse event; AUC = area under the curve; C_{max} = maximum concentration of drug; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; FAS = Full Analysis Set; NCI = National Cancer Institute; OR = objective response; PAS = Pharmacokinetics Analysis Set; PD = pharmacodynamics; PK = pharmacokinetics; PR = partial response; RP2D = recommended Phase 2 dose; SAS = Safety Analysis Set; $t_{1/2}$ = half-life.

10.2. Selection of Sample Size

Approximately 63 eligible subjects (Up 30 in Dose Escalation and up to 33 in Safety Expansion) in Phase 1 will be included in this study.

10.2.1. Sample Size for Dose Escalation

We will employ the Bayesian optimal interval (BOIN) design (Liu 2015; Yuan et al. 2016) to guide dose escalation and establish the MTD or the optimal biologically active recommended Phase 2 dose (RP2D) for NC525.

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size per cohort is 12. We will enroll and treat subjects in cohorts of size 3. DLTs are defined in Section 5.9. The steps to implement the BOIN design are described as follows:

1. To minimize the chance of exposing subjects to potentially subtherapeutic doses, perform the accelerated titration at dose level 1 (DL1) as follows: treat the first subject at DL1, if a DLT or two or more grade 2 toxicities are observed, treat 2 additional subjects at DL1; otherwise escalate to DL2 and hereafter treat subjects in cohort size of 3.
2. To assign a dose to the next cohort of subjects, conduct dose escalation/de-escalation according to the rule displayed in Table 1 (or equivalently Figure 2). When using Table 1/Figure 3, please note the following:
    - If the criteria is met to escalate the dose, dose escalation will be evaluated against the Dose Increment Modification Rule (Table 2).
    - "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future subjects at these doses because they are overly toxic.
    - When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    - If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new subjects at the current dose.
    - If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new subjects at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
    - If the current dose is the highest dose and the rule indicates dose escalation, treat the new subjects at the highest dose.
3. Repeat step 2 until the maximum sample size of 30 is reached or stop the trial if the number of evaluable subjects treated at the current dose reaches 9 and the decision according to the rules described in Step 2 is to stay at the current dose.

The sample size of dose escalation is not based on conventional power calculation, but chosen to be consistent with typical phase I oncology trials and calibrated using simulation. Below provides the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app "BOIN" (BOIN V2.7.6.0), showing that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.

Table 14: Operating characteristics of the BOIN design

	Dose Level					Number of Patients	% Early Stopping
	1	2	3	4	5		
Scenario 1							
True DLT Rate	**0.25**	0.41	0.45	0.49	0.53		
Selection %	**67.6**	16.9	6	1.4	0.2		7.9
% Pts Treated	**43.5**	34.3	17.6	3.9	0.7	18.4	
Scenario 2							
True DLT Rate	0.12	**0.25**	0.42	0.49	0.55		
Selection %	25.9	**53.5**	16.9	2.8	0.2		0.7
% Pts Treated	24.2	**41.1**	27.1	6.4	1.1	21.2	
Scenario 3							
True DLT Rate	0.04	0.12	**0.25**	0.43	0.63		
Selection %	1.8	23.8	**60.5**	13.5	0.4		0
% Pts Treated	8.4	25.7	**41.8**	20.6	3.4	22.1	
Scenario 4							
True DLT Rate	0.02	0.06	0.1	**0.25**	0.4		
Selection %	0.3	2.3	21.4	**58.3**	17.7		0
% Pts Treated	5.3	8.6	30.3	**37.3**	18.5	22.9	
Scenario 5							
True DLT Rate	0.02	0.05	0.08	0.11	**0.25**		
Selection %	0.5	0.9	7.3	22.1	**69.2**		0
% Pts Treated	5.2	7.5	20.6	30.4	**36.4**	21.6	

Note: "% Early Stopping"" refers to early stopping due to excessive DLT.

10.2.2. Sample Size for Safety Expansion

After the dose escalation is completed, select the MTD based on isotonic regression as specified (Liu 2015).

To better characterize and optimize RP2D, depending on the toxicity and PK/PD data, backfill (up to 6 additional subjects per dose) could start during the dose escalation given the dose has been deemed tolerable by the design, and could be performed at more than two doses.

After Dose Escalation has been completed, safety expansion up to 14 subjects per dose (including subjects treated at that dose level in the dose escalation phase) will be performed.

The doses for safety expansion are required to be no higher than the MTD and show sufficient PK/PD and anti-leukemic activities. The RP2D will be chosen based on an overall assessment of DLTs, safety profile, subject tolerance, biological activities and clinical efficacy signals collected at all different doses tested. The RP2D is required to be no higher than the MTD. A Bayesian toxicity monitoring rule will be used to ensure safety during safety expansion. At the RP2D, if 3 or more responses are observed, up to an additional 14 subjects may be enrolled to further evaluate its antitumor activities, safety and tolerability. Among the total of 28 subjects at the RP2D, if 9 or more responses are observed, the treatment is regarded as promising.

At the RP2D, the futility stopping rule (i.e., the safety expansion is subject to potential termination if 2 or fewer responses are observed among the first 14 subjects) yields the operating characteristics listed in Table 15 based on simulation.

Table 15: Futility Stopping Rule

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.2	44.81	8.67	21.7
2	0.4	3.98	84.06	27.4
3	0.5	0.65	97.84	27.9

During safety expansion, we monitor toxicity using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee, and Yuan 2017). Table 16 below provides the stopping boundaries of the BOP2 design.

Table 16: Optimized Stopping Boundaries

No. of subjects treated	Stop if no. of toxicity >=
6	2
12	4
18	5
28	7

If the stopping boundaries are crossed, the subject accrual to that dose will be halted and the totality of safety data will be reviewed for potential termination of that dose.

Let $\boldsymbol{p_{tox}}$ denote the true toxicity rate, the above stopping rule is obtained by maximizing Pr (claim that the treatment is safe | $\boldsymbol{p_{tox} = 0.15}$), while controlling Pr(claim that the treatment is safe | $\boldsymbol{p_{tox} = 0.25}$) $\leq$ 0.3, based on the following Bayesian stopping rule: the treatment is deemed unacceptably toxic if

$$\boldsymbol{Pr(p_{tox} \leq 0.25 | data) < \lambda \left(\frac{n}{N}\right)^{\alpha/3}},$$

where, n is the interim sample size, N is the maximum sample size, and λ=0.55 and α=0.07 are design parameters optimized, assuming a vague prior Beta(0.25, 0.75) for p_{tox} to make "go/no-go" decision. Note that the original publication of the design used the probability cutoff $\lambda(n/N)^{\alpha}$, here the attenuation factor 3 is added (i.e., α/3) to obtain stricter interim stopping boundaries to enhance safety.

Below in Table 17 are the operating characteristics of the design based on 10,000 simulations.

Table 17: Operating Characteristics

Scenario	Toxicity Rate	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.33	84.03	7.99	11.3
2	0.25	62.85	27.97	15.7
3	0.15	27.64	69.63	22.4
4	0.05	3.38	96.61	27.3

Note: Since NC525 is a humanized monoclonal antibody, infusion reactions may occur. Furthermore, treatment of advanced myeloid neoplasms may cause differentiation syndrome and tumor lysis syndrome. Therefore, such events will be categorized as ECIs. Although these events may contribute to Dose Limiting Toxicities, they will be excluded when calculating the toxicity rate for evaluation of the stopping rule, except for Grade ≥ 3 differentiation syndrome that has not resolved within 7 days. All other events as defined in the DLT Table (Table 6) will be used as the criteria to evaluate the severe toxicity rate in the calculation of the stopping rule.

10.3. Statistical Analyses

10.3.1. Safety Analyses

All the safety data in the SAS will be summarized and listed by dose level and cohort.

10.3.1.1. Adverse Events

A treatment-emergent adverse event (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v5.0 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered treatment-related AEs (TRAEs). If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment related. The incidence, frequency, duration, and severity of all AEs (regardless of causality) will be tabulated.

10.3.2. PK Analyses

The PK analyses will be based off the PAS, and PK time-concentration data will be summarized, listed, and plotted. PK parameters ($AUC_{0\text{-}168}$, $AUC_{0\text{-}\infty}$, C_{max}, $t_{½}$, etc.) derived from time-concentration data will be summarized.

10.3.3. Pharmacodynamic and Biomarkers Analysis

The PD and biomarkers are explorative for this study. These data will be listed only.

Descriptive statistics will be the primary methods for the exploratory analyses. Among the variables to be included in the exploratory analyses are:

- Correlation analysis between PD biomarkers and the disease response to treatment with NC525.

The immunogenic potential of NC525 will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. The impact of ADAs on PK will be assessed if data allow. Samples will be collected for evaluating neutralizing capacity of ADAs in the future.

11. STUDY AND DATA MANAGEMENT

11.1. Training of Study Site Personnel

Before the first subject is entered into the study, a NextCure representative will review and discuss the requirements of this protocol and related documents with the investigational staff and train them in any study-specific procedures and system(s) utilized.

The Principal Investigator (PI) will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

11.2. Monitoring of the Study

During the study, a NextCure representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, and that biological samples are handled in accordance with the Central Laboratory Manual
- That study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The NextCure representative will be available between visits if the investigator(s) or other staff at the center needs information or advice about the study conduct.

11.2.1. Source Data

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the eCRF derived from source documents should be consistent with the source documents.

The primary source document for this study will be the subject's medical record. If the investigator(s) maintains separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Data recorded on source documents will be entered into eCRFs. The investigator must promptly review the completed eCRFs for each subject. A study monitor representing the sponsor will review the source documents against the eCRF on a regular basis throughout the study.

The PI at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of the protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between NextCure and the PI must be in place before any study-related procedures can take place, or subjects are enrolled.

11.2.2. Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement and according to the ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after the study is discontinued and the FDA is notified.

11.3. Study Timetable and End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

11.4. Data Management

Data management will be performed according to the study specific supplemental Data Management Plan.

A web based Electronic Data Capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

11.5. Medical Monitor Coverage

Each subject will be provided with contact information for the PI and the site coordinator(s). In an emergent situation, a subject may present to a medical facility where the treating health care provider is not involved with this clinical trial. The treating healthcare provider may require additional information on the study drug, and the subject should provide contact information for the site coordinator(s) or the PI.

The PI will then be required to update the medical monitor.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice (GCP), and applicable regulatory requirements.

12.2. Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The anonymity of subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on eCRFs, and other documents submitted to the sponsor. Documents that identify the subject beyond initials and subject number will not be submitted to the sponsor (e.g., the signed ICF) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, site monitor, or sponsor representatives.

NextCure will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent any genetic data being linked to the identity of the subject (if applicable). In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a NextCure medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

12.3. Regulatory Review

An IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects.

The opinion of the IRB should be given in writing. Written approval must be received by the sponsor or designee before enrollment of any subject into the study.

The IRB should approve all advertising used to recruit subjects for the study.

The sponsor or designee should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The sponsor or designee will handle the distribution of any of these documents to the national regulatory authorities.

The sponsor or designee will provide Regulatory Authorities, IRB, and PIs with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

IRBs must be informed of:

- Changes in informed consent
- Revisions of other documents originally submitted for review
- Serious and/or unexpected AEs occurring during the study
- New information that may adversely affect the safety of subjects or the conduct of the study
- Annual update and/or request for re-approval
- Study termination or completion

12.4. Informed Consent

A copy of the proposed ICF must be submitted to the sponsor for review and comment prior to submission to the reviewing IRB. The ICF must be approved by the IRB and contain all elements required by national, state, local and institutional regulations, or requirements.

The PI at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject voluntarily provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB

12.5. Changes to the Protocol and Informed Consent Form

Protocol revisions will be prepared and approved by NextCure and the medical monitor. Minor revisions will be submitted as administrative changes. If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

All protocol amendments will be signed by the PI and approved by the relevant IRB and if applicable, also the national regulatory authority approval, before implementation. Local

requirements are to be followed for revised protocols. Documentation of IRB/ IEC approval must be forwarded to the sponsor, or sponsor's delegate.

The sponsor or designee will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to IRB see Section 12.3.

If a protocol amendment alters the study design, increases potential risk to the subject or otherwise affects statements in the ICF, the ICF must be revised accordingly and submitted to the sponsor or designee and the IRB for review and approval before the revised ICF is used. The approved ICF must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

If local regulations require, any administrative change will be communicated to or approved by each IRB.

12.6. Audits and Inspections

Authorized representatives of NextCure, a regulatory authority, or an IRB may perform audits or inspections at the clinical sites, including source data verification. The purpose of an audit or inspection is to examine all study-related activities and documents systematically and independently, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact NextCure immediately if contacted by a regulatory agency about an inspection at the site.

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SIGNATURES

Sponsor Signature(s)

A PHASE 1, OPEN-LABEL, SAFETY, TOLERABILITY, AND EFFICACY STUDY OF NC525 IN SUBJECTS WITH ADVANCED MYELOID NEOPLASMS

I agree to the terms of this protocol.

[redacted]

_____

Signature and date

[redacted]

Sponsor Signature(s)

A PHASE 1, OPEN-LABEL, SAFETY, TOLERABILITY, AND EFFICACY STUDY OF NC525 IN SUBJECTS WITH ADVANCED MYELOID NEOPLASMS

I agree to the terms of this protocol.

_____

Signature and date

Signature of Principal Investigator

A PHASE 1, OPEN-LABEL, SAFETY, TOLERABILITY, AND EFFICACY STUDY OF NC525 IN SUBJECTS WITH ADVANCED MYELOID NEOPLASMS

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board (IRB).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB and must be approved by the IRB prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

_____

Telephone number: _____

Site/Center Number (if available) _____

APPENDIX 1: ADDITIONAL SAFETY GUIDANCE

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (e.g., the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (e.g., death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (i.e., SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related:	The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject 's medical record.
Not protocol related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject 's medical record).

APPENDIX 2: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE AND FOOD AND ALLERGY ANAPHYLAXIS NETWORK GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

National Institute of Allergy and Infectious Disease (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al. 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

- Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours):

- Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure
- Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

APPENDIX 3: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Eastern Cooperative Oncology Group (ECOG)
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

(Oken et al. 1982)

APPENDIX 4. TUMOR LYSIS SYNDROME CLASSIFICATION

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome*	Criteria for Classification of Clinical Tumor Lysis Syndrome**
Hyperuricemia	Uric acid > 8 mg/dL (475.8 μmol/liter)	N/A
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter)	N/A
Hyperkalemia	Potassium > 6 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 1.12 mg/dL (0.3 mmol/liter)[#]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (Tetany, paresthesia's, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute Kidney Injury[!]	N/A	Increase in the serum creatinine level of 0.3 mg/dL (26.5 μmol/liter) or the presence of oliguria (average urine output of < 0.5 mL/kg/hr over a 6-hour period)

* Laboratory TLS requires two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.

** Clinical TLS requires the presence of Laboratory TLS plus one or more findings from the Clinical TLS column.

Corrected calcium = measured calcium level in mg/dL + 0.8 × (4 − albumin in gm/dL).

! Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

* Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 μmol/L; ≥ 12 to < 16 years, both male and female, 88 μmol/L; ≥ 16 years, female 105.6 μmol/L, male 114.4 μmol/L.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Cross reference: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

APPENDIX 5. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME (TLS)

Abnormality	**Management Recommendations**
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesia's, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.
Abnormality	**Management Recommendations**

Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 μmol/L)	• Consider rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 μmol/L) OR Uric acid ≥ 8.0 mg/dL (476 μmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis
Abnormality	**Management Recommendations**
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 – 2 hours STAT.

APPENDIX 6: OUTCOME MEASURES (EUROPEAN LEUKEMIA NET (ELN) 2022, BLOOD JULY 2022 (ONLINE VERSION)

Outcome measures for clinical trials in acute myeloid leukemia

Category	Definition
Early death	Death from any cause within a timeframe relevant for the therapy being investigated (e.g., 30 and 60 days from commencing therapy)
Overall survival	Defined for all patients in a trial; measured from day 1 of randomization or day 1 of registration in non-randomized trials (or from the date of diagnosis, e.g., for correlative science studies) to the date of death from any cause; patients not known to have died at last follow-up are censored on the date they were last known to be alive
Event-free survival (EFS)	Defined for all patients in a trial; measured from day 1 of randomization or day 1 of registration in non-randomized trials to the date of treatment failure, hematologic relapse from CR/CRh/CRi or death from any cause, whichever occurs first; treatment failure is defined as not achieving either CR, CRh or CRi by a pre-defined landmark (e.g., after two cycles of intensive chemotherapy or 180 days for non-intensive therapy); patients evaluable for response but not achieving either CR, CRh or CRi by the defined landmark and patients who die before the defined landmark without response assessments are considered an event at day 1 of randomization; patients alive who are non-evaluable for response should be censored at day 1 of the randomization; patients achieving either CR, CRh or CRi by the defined landmark but do not relapse or die should be censored on the date they were last assessed for response
Relapse-free survival (RFS)[a]	Defined only for patients achieving complete remission CR, CRh, or CRi; measured from the date of achievement of remission until the date of hematologic relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last known to be alive
Cumulative incidence of relapse (CIR)	Defined for all patients achieving CR, CRh, CRi; measured from the date of achievement of a remission until the date of hematologic relapse; patients not known to have relapsed are censored on the date they were last assessed for response; patients who died without relapse are counted as a competing cause of failure
Cumulative incidence of death (CID)	Defined for all patients achieving CR, CRh, CRi; measured from the date of achievement of a remission to death without prior relapse; relapse is considered as competing risk

[a] Relapse-free and disease-free survival have been used with the same definition.

APPENDIX 7: NC525 STUDY DRUG ADMINISTRATION GUIDANCE

NC525 Dose Calculation (e.g., 80kg Subject)	**Infusion time**	**100ml** 0.9% sodium chloride injection USP (containing no preservatives)	**250ml** 0.9% sodium chloride injection USP (containing no preservatives)
2mg/kg	30 minutes	Total Dose: 160mg Drug Concentration per ml: 1.6mg/ml	
2.5mg/kg	60 minutes	Total Dose: 200mg Drug Concentration per ml: 2.0mg/ml	
4.5mg/kg	120 minutes	Total Dose: 360mg Drug Concentration per ml: 3.6mg/ml	
10mg/kg	TBD	Total Dose: 800mg Drug Concentration per ml: 8mg/ml	
20mg/kg	TBD	Total Dose: 1600mg Drug Concentration per ml: 16mg/ml	
30mg/kg	TBD		Total Dose: 2400mg Drug Concentration per ml: 9.6mg/ml

Note: In the event of an infusion reaction, stop the infusion, and treat appropriately per the infusion reaction guidance in Table 5. If two subjects within a given cohort develop grade ≥ 2 signs or symptoms of infusion reactions, all future subjects must be premedicated.

Note: In all drug dose level calculations, the final infusion concentration must be at or above 0.4 mg/mL and no more than 20 mg/mL.

APPENDIX 8: WEIGHT-BASED DOSING CALCULATION CONSIDERATIONS

Dosing will be based on subject's actual weight (or ideal body weight if considered obese) in kilograms. For the purpose of dose calculations for NC525, the site should determine and evaluate obesity based on institutional guidelines.

Below provides a general reference for Calculation of Ideal Body Weight (IBW) and Obesity Calculation if needed.

Calculation of Ideal Body Weight (IBW)

IBW in kg

Males = 50 + [2.3 x each inch over 5 ft]

or 50 + [2.3 kg x (each cm over 152.4/2.54)]

Females = 45.5 + [2.3 x each inch over 5 ft]

or 45.5 + [2.3 kg x (each cm over 152.4/2.54)]

Calculation for Obesity

[(actual wt - IBW)/IBW]*100%.

If this value is >30% then the person is obese and ideal body weight should be used for weight-based dosing calculations instead of actual body weight.

SUMMARY OF CHANGES

Summary of Protocol Changes

Protocol Version	Date
Version 1.0 (Original)	15-Sep-2022
Version 1.1	25-Oct-2022
Version 1.2	27-Oct-2022
Version 1.3	28-Oct-2022
Version 2.0	26-Apr-2023
Version 3.0	19-Jul-2023
Version 4.0	16-Oct-2023