

Title:

A PHASE 1/2, OPEN-LABEL, DOSE-ESCALATION, SAFETY AND TOLERABILITY  
STUDY OF NC410 IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS

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**A PHASE 1/2, OPEN-LABEL, DOSE-ESCALATION, SAFETY AND  
TOLERABILITY STUDY OF NC410 IN SUBJECTS WITH ADVANCED  
OR METASTATIC SOLID TUMORS**

**Sponsor Protocol Number:** NC410-01  
**IND Number:** 141990  
**Investigational Product:** NC410  
LAIR-2 IgG1 Fusion Protein

**Phase of Study:** 1/2  
**Sponsor:** NextCure, Inc.  
9000 Virginia Manor Road, Suite 200  
Beltsville, MD 20705 USA  
Phone: 240-399-4900  
Email: NCclin@nextcure.com

**Medical Monitor:** Han Myint, MD, FACP, FRCP, FRCPath  
Chief Medical Officer  
NextCure, Inc.  
Phone: 240-399-4900  
Email: NCclin@nextcure.com

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## Protocol Synopsis

### TITLE

A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC410 in Subjects with Advanced or Metastatic Solid Tumors

### HYPOTHESES

NC410 will be adequately tolerated following administration in multiple ascending doses to subjects with refractory solid tumors and that such administration may result in clinical benefit.

### OBJECTIVES

#### Primary Objectives

- 1) To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of NC410
- 2) To define a maximum tolerated dose (MTD) or pharmacologically active dose (PAD) of NC410

#### Secondary Objectives

- 1) To evaluate the pharmacokinetic (PK) profile of NC410
- 2) To assess preliminary efficacy of NC410

#### Exploratory Objectives

- 1) To assess the immunogenicity of NC410
- 2) To explore biomarkers that may predict the pharmacologic activity of NC410
- 3) To characterize the effect of NC410 on markers of immunity

### STUDY ENDPOINTS

#### Primary Endpoints

- 1) Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) **Note:** Toxicity grading per NCI CTCAE v5.0
- 2) The MTD or PAD of NC410 will be defined in subjects with advanced or metastatic solid tumors

#### Secondary Endpoints

- 1) Assessment of PK of NC410 will include individual NC410 concentrations in serum and identification of PK parameters.
- 2) Assessment of antitumor activity/efficacy will include objective response (OR) and disease control rate (DCR) based on RECIST v1.1, duration of response (DoR),

progression-free survival (PFS), and overall survival (OS) as per RECIST v1.1 and mRECIST v1.1

### **Exploratory Endpoints**

- 1) Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC410, will be determined.
- 2) Biomarker effects of NC410 in peripheral blood and tumor tissue will be assessed, including but not limited to the following:
  - Whole blood immune cell population profiling/immune-phenotyping.
  - Serum markers of inflammation or immune modulation (cytokine levels).
  - Tumor biopsy analyses to evaluate the tumor microenvironment in tumor tissue and immune cell infiltrates at baseline, following treatment, and correlate expression levels with efficacy. The expression of additional biomarkers will also be assessed.

### **STUDY DESIGN**

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety and tolerability, define the MTD or PAD, and to assess the preliminary efficacy of NC410 in subjects with advanced or metastatic solid tumors. Subjects will receive NC410 on Day 1 of each cycle. Phase 1 of the study will begin with 14-day cycles; however, alternate dose administration schedules may also be explored depending on PK, pharmacodynamic (PD), biomarker, safety results, and feedback from investigators. The study will be conducted in 2 parts:

- **Phase 1** – Dose Escalation and Safety Expansion will determine the PAD, defined as a dose that provides a maximal biologic effect, such as an increase in biomarkers of immune activation or reduction of markers associated with immunosuppression, and/or the MTD of NC410, including defining the optimal dose administration schedule and the maximum number of tolerated doses (MNTD).
- **Phase 2** – Dose Expansion will evaluate the recommended dose and administration schedule determined in Phase 1 in subjects with Head and Neck squamous cell carcinoma, non-small cell lung cancer (NSCLC) (adenocarcinoma), Colo-rectal carcinoma (CRC), gastric, and cervical cancers. These proposed indications may change based on emerging data.

#### **Phase 1a – Dose Escalation**

In Phase 1a, subjects with advanced or metastatic solid tumors who progressed after treatment with therapies known to confer clinical benefit, are intolerant to treatment, or refuse standard treatment will be enrolled. A 3 + 3 design will be utilized to determine the MTD of NC410.

A minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (3 mg; starting dose). The first 3 evaluable subjects within a cohort will be observed for a DLT observation period of 28 days, before the next cohort begins enrollment. Only one subject will be dosed on the first day of dosing for each cohort (additional subjects can begin in  $\geq 48$  hours). The dose will be escalated if 0 of the first 3 evaluable subjects enrolled has a DLT. If 1 of the first 3 evaluable subjects enrolled has a DLT, then the cohort will be expanded to include 3 additional evaluable subjects, and if no DLT occurs in the additional 3 subjects, then the dose will be escalated. If a DLT occurs in one-third or more of the expanded cohort, then

the MTD will be deemed to be exceeded and the previous dose level will be considered the MTD. Intermediate dose levels below the MTD may be explored pending safety review. If only 3 subjects were treated at the MTD or PAD, then a minimum of 3 additional evaluable subjects will be enrolled at this dose before it is administered in Phase 2 of the study.

If Cohorts exceed the MTD, the sponsor and investigators will consider dosing NC410 at the lower dose cohorts, and/or investigate 3 mg at alternate dose schedules, based on available safety, PK, PD, and biomarker data. If an alternate schedule is determined to be safe, re-escalation of NC410 will proceed according to the table below.

Throughout the treatment period, if  $> 33\%$  of subjects (a minimum of 6 subjects) experience a  $\geq$  Grade 3 toxicity related to study drug after completing  $\geq 4$  cycles, then dose administration will be stopped, and the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Subjects who drop out for reasons other than a DLT (e.g., events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity) during the 28-day DLT observation period will be considered non-evaluable and will be replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted; however, once the recommended Phase 2 dose (RP2D) and schedule has been determined, ongoing subjects in Phase 1 may be permitted to escalate to the RP2D with approval of the medical monitor assuming the subject has not experienced  $\geq$  Grade 3 toxicity in previous treatment cycles. The cohorts and dose levels are shown in the table below.

Cohort	Dose of NC410
1 (Starting dose)	3.0 mg
2	6.0 mg
3	15 mg
4	30 mg
5	60 mg
6	100 mg
7	200 mg
8	400 mg

### Phase 1b – Safety Expansion

To evaluate additional PD activity of NC410 and confirm the preliminary safety of the dose escalation cohorts, Phase 1 of the study will include safety expansion cohorts (denoted as Phase 1b) evaluating doses and schedules equivalent to or lower than the highest dose levels determined to be safe and/or doses determined to be pharmacologically active. All doses and schedules explored during the safety expansion will depend on PK, PD, biomarker, and safety results.

Approximately 30 evaluable subjects will be enrolled in the Phase 1b safety expansion, with each dose cohort enrolling up to 10 additional subjects. If  $< 3$  of 9 evaluable subjects

experience a DLT, the cohort will be deemed safe. If > 1 safety expansion cohort is deemed safe, then a recommended dose and schedule will be determined in conjunction with the investigators and sponsor based on all available safety, PK, PD, and biomarker results. The safety expansion cohorts may be conducted in parallel to Phase 2 and may be limited by the sponsor to subjects with specific tumor types to achieve a balance across cohorts.

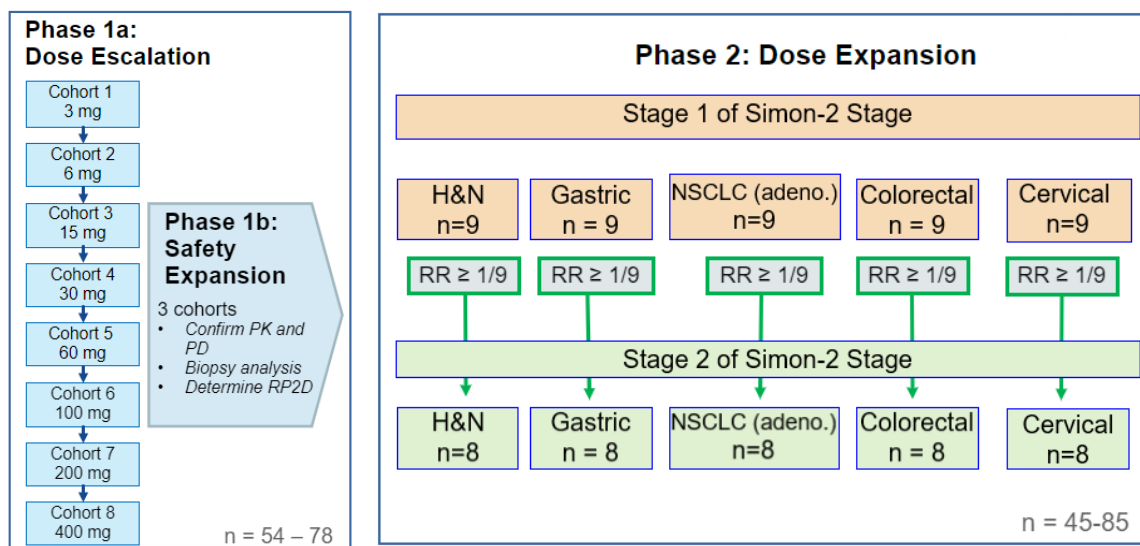
## Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the RP2D of NC410 in subjects with advanced or metastatic HNSCC, NSCLC (adenocarcinoma), CRC, gastric, and cervical cancers. A sixth cohort may be included and will enroll patients of a tumor type pending outcomes of Phase 1a. A Simon 2-stage design will be utilized with a stopping rule to allow for early termination of a cohort at the end of Stage 1 if there are insufficient responses observed. During Stage 1, 9 evaluable subjects will be enrolled in each cohort; if no responses are observed within the cohort then the cohort will be discontinued. If at least 1 response is observed, 8 additional evaluable subjects will be enrolled in the cohort (Stage 2), for at least 17 evaluable subjects per cohort.

Subjects will continue to receive NC410 at the RP2D and schedule until protocol-defined withdrawal criteria are met. Continuous evaluation of toxicity events will be performed throughout enrollment in Phase 2 of the study. If the cumulative incidence of DLTs occurs in  $\geq 33\%$  of subjects after 6 subjects have been observed for at least 28 days, further enrollment may be interrupted until the sponsor has determined the appropriate course of action. All AEs, regardless of the time of occurrence on study may be considered in determining the appropriate dose, schedule, and MNTD.

Toxicity will continue to be monitored throughout the treatment period. If > 33% of subjects (minimum of 6 subjects) experience a  $\geq$  Grade 3 toxicity related to study drug after completing  $\geq 4$  cycles, then the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

## Study Schema



RR = Response Rate (ORR) per RECIST v1.1

### **TARGET SUBJECT POPULATION**

Men and women, 18 years or older, with advanced solid malignancies who have progressed on standard treatment, who have been unable to tolerate standard therapy, who have refused standard therapy, or for whom no standard anticancer therapy exists may be enrolled. Subjects must provide written informed consent and have adequate organ function. Subjects must present with measurable disease based on RECIST v1.1 and consent to have a non-target lesion biopsied before and during treatment. Subjects with certain serious medical conditions (in addition to the diagnosis of cancer) would be excluded from participation in the trial.

### **INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION**

NC410 will be administered by intravenous (iv) infusion, over a minimum of 30 minutes on Day 1 of each cycle. Subjects will continue to receive NC410 until disease progression, withdraw of consent, or intolerable toxicity (whichever comes first). After completing 12 months of treatment, if the subject is deriving benefit from NC410 and has not met any of the protocol-defined conditions for withdrawal or discontinuation, the subject will be followed by the PI per standard of care. Subjects approved to continue treatment will remain on the dose level assigned at the time of enrollment (unless otherwise approved for dose modification by the medical monitor). Safety reporting will continue through end of treatment to completion of the safety follow-up period.

### **STATISTICAL ANALYSIS PLAN**

The sample size for this study will be determined so that sufficient subjects are included to assess the safety, tolerability, PK, and PD of repeat doses of NC410. The sample size is not fixed and will vary based on emerging safety data at the doses studied.

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## List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BSA	Body Surface Area
C <sub>max</sub>	Maximum Concentration of Drug
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTLA-4	Cytotoxic T-Lymphocyte–Associated Protein 4
DC	Dendritic cell
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
EC <sub>30</sub>	Effective Concentration for 30% of Maximum Effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End-of-Treatment
FAAN	Food and Allergy Anaphylaxis Network
FAS	Full Analysis Set
Fc	Fragment crystallizable
FIH	First-in-Human
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practices



<b>Abbreviation or Specialized Term</b>	<b>Definition</b>
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HNSTD	Highest Non-Severely Toxic Dose
HPV	Human Papillomavirus
IB	Investigator's Brochure
IBW	Ideal Body Weight
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalized Ratio
INs	Investigator Notifications
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
iv	Intravenous
LAIR	Leukocyte-Associated Immunoglobulin-like Receptor
LKA	Last Known Alive
LPS	Lipopolysaccharide
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MNTD	Maximum Number of Tolerated Doses
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Disease
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
ORR	Objective Response Rate

<b>Abbreviation or Specialized Term</b>	<b>Definition</b>
OR	Objective Response
OS	Overall Survival
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 Response
PT	Prothrombin Time
QTcF	Fridericia Correction
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SSD	Safe Starting Dose
$t_{1/2}$	Half-Life
TEAE	Treatment-Emergent Adverse Event
TK	Toxicokinetic
TME	Tumor Microenvironment
TNBC	Triple Negative Breast Cancer
TPS	Tumor Proportion Score
Treg	Regulatory T cell
ULN	Upper Limit of Normal
US FDA	United States Food and Drug Administration
USA	United States of America

# 1 INTRODUCTION

This is a Phase 1/2, multicenter, open-label, dose-escalation study. The study will be conducted in 2 parts. Phase 1 will utilize a 3 + 3 design to determine the maximum tolerated dose (MTD) or pharmacologically active dose (PAD) for NC410 in subjects with advanced or metastatic solid tumors. Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of the recommended Phase 2 dose (RP2D) and administration schedule of NC410 in subjects with advanced or metastatic HNSCC, NSCLC (adenocarcinoma), CRC, gastric, and cervical cancers or other tumor type as identified with emerging data.

## 1.1 Background

### 1.1.1 Role of tumor microenvironment in immune surveillance

The tumor microenvironment (TME) of solid tumors are a complex heterogeneous mixture of matrix components and neoplastic cells along with different non-cancerous cell types such as fibroblasts, vascular endothelial cells, and immune cells, including T-cells, macrophages, and neutrophils, collectively known as tumor stroma. The interaction of cancer cells with stromal cells is a crucial determinant of tumor clearance versus progression, thus shaping tumor evolution.

Cancer cells are under continuous pressure to thwart immune responses through activation of negative costimulatory signaling, impairment of antigen presentation, and secretion of immunosuppressive and pro-apoptotic factors. The dynamic state of the TME was demonstrated in breast tumor progression by comparing ductal carcinoma in situ (DCIS) and invasive ductal carcinomas (IDC) wherein there was fewer activated CD8+ T cells and higher programmed cell death protein ligand 1 (PD-L1) expression in IDC ([Gil Del Alcazar et al., 2017](#)). The presence of regulatory T cells (Tregs) in the TME is also a driver of immunosuppression. A detailed analysis of CD8+ T cell along with ratio of CD8+ effector T cell to Tregs show significant correlation to improved patient prognosis and long-term survival in many solid tumors ([Kirk, 2010](#); [Nosho et al., 2010](#); [Liu et al., 2011](#); [Mathai et al., 2012](#); [Yoon et al., 2012](#); [Preston et al., 2013](#); [Chang et al., 2014](#); [Kim et al., 2014](#)). Myeloid-derived suppressor cells (MDSCs) within the TME also drive tumor growth, angiogenesis, metastasis and immune evasion ([Yang et al., 2004](#); [Yang et al., 2008](#); [Gabrilovich & Nagaraj, 2009](#); [Khaled et al., 2013](#)). In melanoma patients, circulating MDSCs correlate to poor clinical outcome upon treatment with ipilimumab ([Meyer et al., 2014](#)). Disruption of CXCR2-mediated trafficking of MDSCs to the TME in a murine model of rhabdomyosarcoma enhanced efficacy of anti-PD1 therapy, further validating MDSC mediated immune suppression ([Highfill et al., 2014](#)). Tumor-associated M2-like macrophages (TAMs) also play a role in promoting tumor progression in the TME ([Lewis & Pollard, 2006](#)). Their immunosuppressive effects are supported in several different murine models ([Fritz et al., 2014](#); [Wu et al., 2014](#); [Zhu et al., 2014](#); [Ruffell & Coussens, 2015](#)). In addition, distinct subsets of dendritic cells may also contribute to the immunosuppressive milieu in the TME.

The matrix of the TME itself also contributes to the pro-tumorigenic environment. For example, many tumor types overexpress matrix components such as collagens and complement component C1q that play an important role in creating a TME; the resulting TME supports tumor cell

survival and metastasis leading to unfavorable clinical outcome. Earlier studies have demonstrated that these components also serve as ligands for a collagen-binding inhibitory receptor known as Leukocyte-Associated Immunoglobulin-like Receptor (LAIR)-1. LAIR-1 ligands include several types of collagen such as complement component C1q, mannose binding lectin (MBL) and surfactant protein-D (SP-D) (Lebbink et al., 2008; Lebbink et al., 2009; Olde Nordkamp et al., 2011; Olde Nordkamp et al., 2014b). Dysregulation of LAIR ligands results in excessive production of collagens and complement C1q as well as altered forms of collagens that may exert strong inhibitory effects in the TME (Afshar-Kharghan, 2017; Pearce et al., 2018). Indeed, published data indicate that tumor expressed collagens inhibit immune function through LAIR-1 (Rygiel et al., 2011). Other factors common to dysregulated tumor environments, such as damage associated molecular patterns (DAMPs), are likely to play supporting roles in mediating the enhanced inhibitory function of LAIR-1 in cancer (Son & Diamond, 2014; Son et al., 2016). Furthermore, it is hypothesized that LAIR-1 expression on several subsets of leukocytes prevents optimal immune responses by limiting both innate and adaptive immune functionality. Overall, these data suggest that targeting the LAIR pathway in cancer patients may be a rational approach in potentiating anti-tumor immunity.

### 1.1.2 Current Immunotherapy

Targeting the immune system to regulate various pro-tumorigenic pathways in the TME is an effective approach for cancer therapy as demonstrated by approved checkpoint inhibitors; these immunotherapies have gained substantial attention in cancer treatment due to the durability of the responses and increased survival benefit. To date, the U.S. Food and Drug Administration (US FDA) has approved seven immune checkpoint inhibitors to date. Approvals includes one CTLA-4 inhibitor (ipilimumab), three PD-1 inhibitors (nivolumab, pembrolizumab, and cemiplimab) and three PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab).

Despite these impressive responses, only 20-30% of patients in specific subsets of tumor types respond to checkpoint inhibitors and can have caveats relating to success. As an example, the prolonged time necessary to achieve a response is not ideal for patients with advanced metastatic disease. Recent efforts to improve upon the initial success of checkpoint inhibitors have focused on combination-based regimens; however, these regimens can have significant toxicity associated with its utilization and are not consistently improving efficacy. Further, it is becoming increasingly clear that there are additional mechanisms at play as patients can have varying responses. Current immunotherapy trials are increasingly incorporating biomarker studies, such as assessing the tumor mutational burden (TMB) and PD-L1 expression. It has been shown that prior exposure to chemotherapy alleviates the effect of TMB on immunotherapy (Hendriks et al., 2018). Taken together, there is a significant gap to bridge towards understanding the modest response rates with checkpoint inhibitors as well as stratification of patients who will benefit from immunotherapy. Therefore, to address the disparity in the number of patients responding to immunotherapy and the degree to which they respond, there is a need to develop immunomodulators with new and alternative mechanisms of action.

### 1.1.3 LAIR-1/2 and Immunity

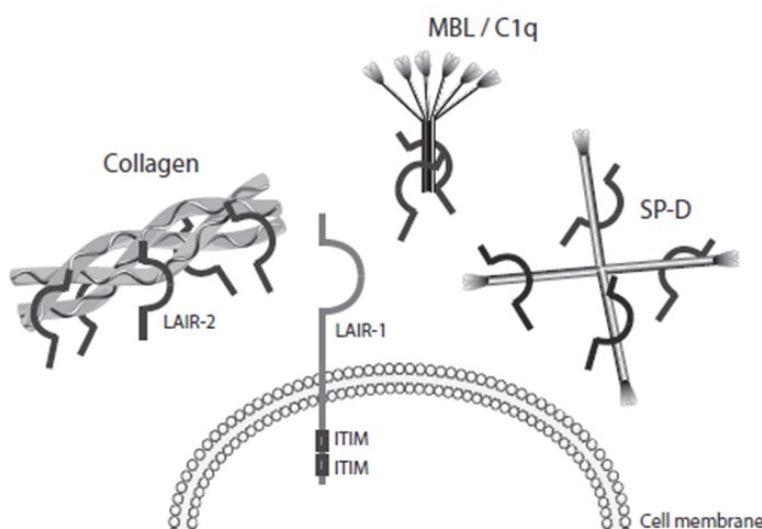
Leukocyte-Associated Immunoglobulin-like Receptor (LAIR)-1 and LAIR-2 are members of the Leukocyte Receptor Complex (LRC) on human chromosome 19 (Trowsdale et al., 2015; An & Brodsky, 2016). LAIR-1 is a well-described co-inhibitory receptor expressed on several subsets

of immune cells, and functions to delimit immune responses (Meyaard et al., 1997; Meyaard et al., 1999; Lebbink et al., 2008). LAIR-2 is a secreted protein with homology to the transmembrane protein LAIR-1 (Lebbink et al., 2008).

In cancer, it is hypothesized that LAIR-1 expression on several subsets of leukocytes prevents optimal immune responses by limiting both innate and adaptive immune functionality. LAIR-1 serves to suppress anti-tumor immunity through the inhibition of stimulatory signaling pathways. Specifically, LAIR-1 is a checkpoint and adhesion receptor on T cells that limits T cell activation and increases adhesion to collagens (Meyaard, 2008). In addition to its role in T cell function, LAIR-1 is also expressed on NK, monocyte, macrophage, dendritic cells and neutrophils and functions to delimit immune responses. Further, LAIR-1 expression has been shown to be associated with suppressive DC and macrophage subpopulations in both mouse and human ovarian cancers (Flies et al., 2016). Blockade of LAIR-1 in cancer should reduce inhibitory mechanisms to redirect myeloid cells toward promoting stimulatory responses, including T cell responses, against tumors.

LAIR-2 is a secreted protein with 77.5% homology in the Ig-like C2 domain of extracellular region to the transmembrane protein LAIR-1 and serves as a natural, endogenous, secreted decoy for LAIR-1 produced primarily by activated T cells (Meyaard, 2008). LAIR-2 is capable of blocking LAIR-1 functional interactions with ligands, resulting in improved immune function on multiple immune cell subsets (Figure 1). Of note is the observation in which dysregulation of LAIR-1 ligands results in excessive production of collagens and complement C1q as well as altered forms of collagens that may exert strong inhibitory effects in the TME (Afshar-Kharghan, 2017; Pearce et al., 2018). Thus, disrupting the interaction of LAIR-1 ligands with LAIR-1 and interrupting the inhibitory effects of the TME utilizing a LAIR-2 based therapy is a novel approach to cancer therapy.

**Figure 1: LAIR-2 is Capable of Immune Regulation Through Blockade of Ligand Binding to the LAIR-1 Receptor to Relieve Immune Suppression**



LAIR-2 binds to collagen, complement C1q, MBL and SP-D, blocks the ligation of LAIR-1 on immune cell surface and relieves the LAIR-1 inhibitory signaling. (figure courtesy of ([Olde Nordkamp, 2013](#)))

#### 1.1.4 Development of NC410

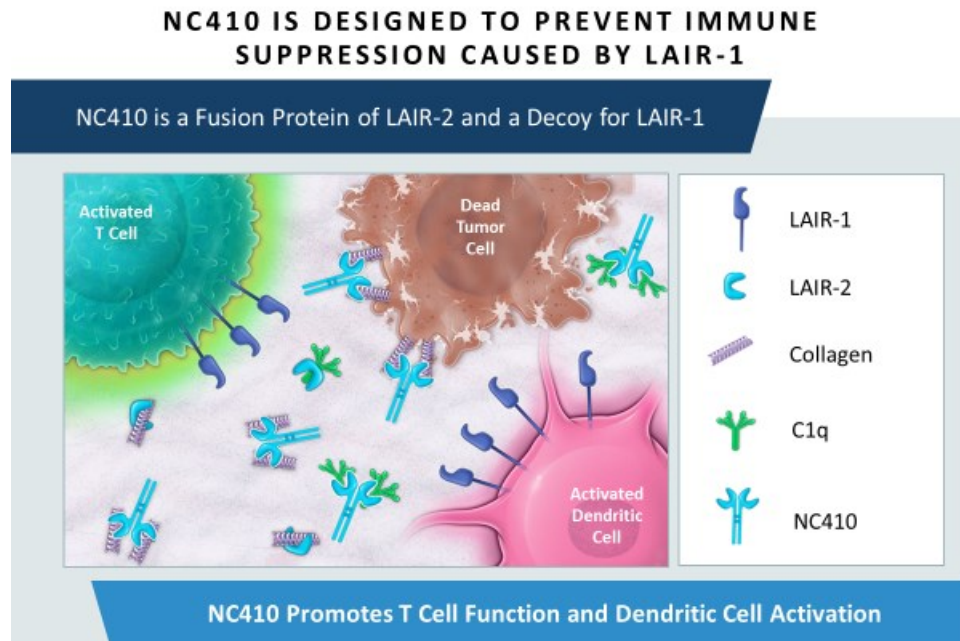
NC410 is a dimeric form of the LAIR-2 protein fused to a human Fc domain of the immunoglobulin (Ig) subtype IgG1. The rationale for developing NC410 as a cancer therapeutic is based on nonclinical data demonstrating LAIR-1 signaling blockade can improve the immune response. Because LAIR-2 binds to ligands shared with LAIR-1 with increased affinity, NC410 can act as a decoy receptor for LAIR-1 ligands with the intent to release the suppression on myeloid cells and T cells. In addition, the collagen binding of NC410 may further facilitate the tumor targeting and accumulation of NC410 within the TME.

NC410 has been studied in a variety of *in vitro* and *in vivo* systems to support its use as an investigational drug in oncology. These studies have demonstrated enhanced immune activity in mechanistic studies and tumor models, as outlined below:

- Binds to LAIR-1 ligands including collagen, C1q, MBL and SP-D with high avidity and block the interaction of LAIR-1 to its ligands.
- Reverses the inhibitory effects of collagen on the Lipopolysaccharide (LPS)-induced NF- $\kappa$ B and Interferon signaling, important signaling pathways leading to immune cell activation.
- Promotes primary monocyte activation and differentiation toward a stimulatory macrophage phenotype induced by HMGB1, the cancer-relevant immune cell stimulator in TME.
- Enhances human T cell expansion and activation in a dose-dependent manner, which correlates to the tumor efficacy in a mouse P815 and human HT29 tumor models and CXCL12 cytokine production.
- Distributes to secondary lymphoid organs and TME

In summary, these studies specifically utilizing human cells, or “humanized models” have demonstrated the most significant increase in immune function and anti-tumor activity in the presence of NC410, supporting its mechanism of action.

**Figure 2: NC410 Binds to Tumor-Associated Ligands to Block LAIR-1 Inhibition**



NC410 binds to tumor-associated ligands (collagen and C1q) to block LAIR-1 inhibition and promote adaptive (T cells) and innate (dendritic cells) immune responses, as well as to activate macrophages, ultimately resulting in tumor cell killing.

## 1.2 Overview of NC410

NC410 is a soluble humanized LAIR-2 protein fused to human IgG1 Fc domain and binds several LAIR ligands, including collagens, C1q, MBL and SP-D. It is a novel immunotherapeutic protein that was developed to enhance the natural decoy mechanism by blocking LAIR-1 mediated immune suppression, thus reversing multiple immune suppressive mechanisms and restoring immune function. NC410 is being developed as an immunotherapeutic agent to treat human oncological diseases.

### 1.2.1 Pharmacokinetics of NC410

The pharmacokinetics (PK) of NC410 were characterized in cynomolgus monkeys as part of single-dose, dose-range-finding and repeat-dose toxicity studies. Because the toxicokinetic (TK) parameters of the cynomolgus monkey studies were determined to be a more pharmacologically relevant species, these results are summarized below. For additional information, please refer to the NC410 Investigator's Brochure (IB).

The pharmacokinetic properties of NC410 were assessed in cynomolgus monkeys in a Good Laboratory Practices (GLP) repeat-dose study. The mean terminal half-life was approximated 55 hours following one IV infusion of NC410 and approximately 60 hours following 5 repeated doses. In the GLP repeat-dose study, there was a dose proportional relationship between dose level and exposure; no gender differences were observed. ADA was detected in animals received multiple doses at 20 mg/kg, which appeared to impact systemic exposure. Immunogenicity of human protein therapeutics in non-human species is a common



occurrence, and immunogenicity data from animals have little value for predicting the risk of immunogenicity in humans, as discussed in International Council for Harmonization (ICH) S6(R1) and (Ponce et al., 2009).

### 1.2.2 Pharmacology of NC410

The pharmacology of NC410 has been studied in a variety of *in vitro* and *in vivo* systems to support its use as an investigational drug in oncology. This section highlights the results of these studies; please consult the NC410 IB for additional information.

NC410 binds to LAIR-1 ligands including collagen, C1q, MBL and SP-D with high avidity and this binding blocks the interaction of soluble and cell surface LAIR-1 to its ligands. Using an immune cell line or primary peripheral blood mononuclear cells (PBMCs), NC410 reverses the inhibitory effects of collagen on the LPS-induced NF- $\kappa$ B and interferon signaling, important signaling pathways leading to immune cell activation. Furthermore, NC410 promotes primary monocyte activation and stimulatory macrophage differentiation induced by HMGB1, the cancer-relevant immune cell stimulator in TME. Employing conditions that would have predicted the high risk of CRS for the anti-CD28 monoclonal antibody (mAb) TGN1412 (Stebbins et al., 2007; Findlay et al., 2010), NC410 did not promote cytokine release relative to a negative control (anti-RSV) (Synagis®).

The *in vivo* efficacy of NC410 was tested in humanized mouse models in which human PBMCs were transferred to NSG mice. NC410 treatment enhanced human T cell expansion and activation in a dose-dependent manner, which correlated with tumor efficacy and CXCL12 cytokine production in a P815 tumor model. Moreover, NC410 dose-dependently reduced the tumor growth of HT-29 human colorectal adenocarcinoma.

A biodistribution study was performed in mice to determine the localization of NC410, as well as the ability of NC410 to access the tumor microenvironment when administered at very low doses. Briefly, NC410 accumulated in the liver and tumor sites was quantitated at 24, 48 and 72 hours in comparison to a positive control mAb. Interestingly, NC410 accessed the tumor similarly to the positive control, which targeted a tumor antigen. While the overall amount of NC410 reaching the tumor is small in comparison to liver, it is similar to the positive control and in line with expectations for a subcutaneous tumor model. These data confirm that NC410 can access the tumor similarly to tumor targeting mAbs, distribute in a non-random fashion to the liver, spleen and lymph nodes, and can access and accumulate in the lymph nodes. Full analysis of this study is described in the NC410 IB.

### 1.2.3 Non-Clinical Safety and Potential Risks of NC410

The toxicology of NC410 has been studied in a variety of *in vitro* and *in vivo* systems to support its use as an investigational drug in oncology. A summary of the GLP toxicity study in which cynomolgus monkeys were administered escalating doses of NC410 are provided below; full results of this study and prior dose toxicity studies are described in the NC410 IB.

The most notable effects of NC410 following five weekly intravenous infusions over 30 minutes to cynomolgus monkeys include a dose-dependent reduction in NK cells at doses  $\geq 2$  mg/kg (with persistence at 20 mg/kg), a transient dose-dependent activation of complement at doses  $\geq 2$



mg/kg and adverse microscopic findings at doses  $\geq 2$  mg/kg, which either completely or partially resolved by the end of the 6-week recovery period. At the 20 mg/kg, these effects were accompanied with secretion of cytokines and chemokines following the first dosing, which subsided over time and was not observed following the 5<sup>th</sup> weekly administration. The cytokine secretion was not observed at the 0.2 or 2 mg/kg dose levels. Routine laboratory tests will include analysis of NK cell population and complement classical pathway activation throughout the conduct of this clinical study.

Based upon the results of the GLP 5-week repeat-dose toxicity study, the highest non-severely toxic dose (HNSTD) was determined to be 20 mg/kg, and the No Observed Adverse Effect Level (NOAEL) was 0.2 mg/kg. These results were used to identify the safe starting dose for the clinical study.

### 1.3 Study Rationale

Immunotherapies have demonstrated an effective anti-tumor immune response and induce significant clinical benefit for a subset of patients with cancer. This study will evaluate targeting the LAIR pathway which through LAIR-1 has been known to limit T cell activation and suppress anti-tumor immunity in the TME. While immunotherapies for cancer have shown great promise, there is still an unmet medical need for additional therapies with novel approaches. Therefore, NC410 may be an effective immunotherapy for some cancer patients.

#### 1.3.1 Rationale for the Safe Starting Dose

The rationale for the proposed Phase 1 starting dose (SSD) of 0.04 mg/kg is based on the collection of preclinical pharmacology and toxicology data, including calculated and experimentally assessed dose-responses in human cell-based assays, and anti-tumor responses in NSG models (NC410 IB). The clinical starting dose is 5-fold less than the NOAEL and 500-fold less than the HNSTD. 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. In the absence of dose-limiting toxicity, the maximum dose that may be explored in the first in human trial will be 5 mg/kg, which is four-fold below the highest non-severely toxic dose (HNSTD) in the GLP-compliant repeat dose tox (20 mg/kg) study in cynomolgus monkeys. Based on the dose dependency of the toxicities identified in the toxicology studies and the large safety margins, the chosen clinical doses are expected to provide therapeutic benefit with minimal safety risk to the patient.

A summary of the pharmacology and toxicology data is provided below:

- NOAEL = 0.2 mg/kg (Study 2823-002, as described in the NC410 IB)
- HNSTD = 20 mg/kg (Study 2823-002, as described in the NC410 IB)
- Minimum anticipated biological effect level (MABEL) EC30 dose = 0.16 mg/kg (described in section 4.1.4.3 of the NC410 IB)
- *In vivo* model in NSG mice, ED50 dose = 0.66 mg/kg (data provided in Figure 16 and section 4.1.5.4 of the NC410 IB)
- Recommended starting dose = 0.04 mg/kg
- Recommended maximum dose = 5 mg/kg

Given the known biology of the LAIR pathway and its relevance in immune function, immune related adverse events (irAE) are the most likely class of toxicity. This clinical protocol has been written to minimize and manage any potential irAEs and any infusion reactions. Eligibility criteria have been established to exclude subjects in the Phase 1 clinical study with a history of autoimmune disease or who may have experienced an unresolved irAE to another immunotherapy.

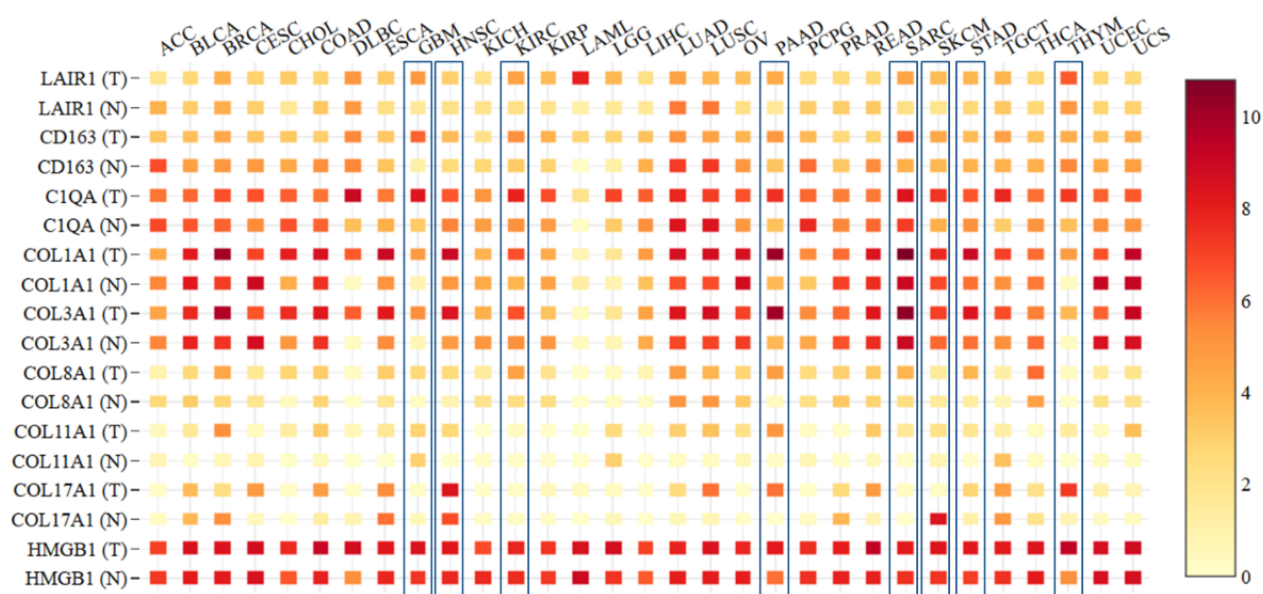
### 1.3.2 Rationale for Fixed Dosing

Fixed dosing has several advantages over weight-based dosing, including convenience of preparation and administration, reducing errors in preparation calculation, and minimization of drug waste. Body size-based dosing and fixed dosing of mAbs have been evaluated with the 2 dosing approaches performing similarly, with body size-based dosing not always offering an advantage in reducing variability of exposure. The authors of these studies concluded that either approach may be used in first-in-human (FIH) studies and that fixed dosing is recommended as the preferred approach because of the advantages mentioned above (Wang et al., 2009; Bai et al., 2012).

### 1.3.3 Rationale for Subject Population for Phase 2

Preliminary identification of tumor types most likely to benefit from NC410 therapy was based on several analyses examining LAIR expression and other factors. Initial selection of relevant tumor types was first determined based upon results of an analysis from The Cancer Genome Atlas (TCGA). Specifically, thirty tumor types were analyzed for RNA expression of LAIR-1 expression, macrophage markers CD163, LAIR-1/2 ligands C1Q and various collagens, and HMBG1 (due to its described role in interacting with C1Q to promote M2 macrophage differentiation through LAIR-1) (Son et al., 2016). These results are summarized in Figure 3.

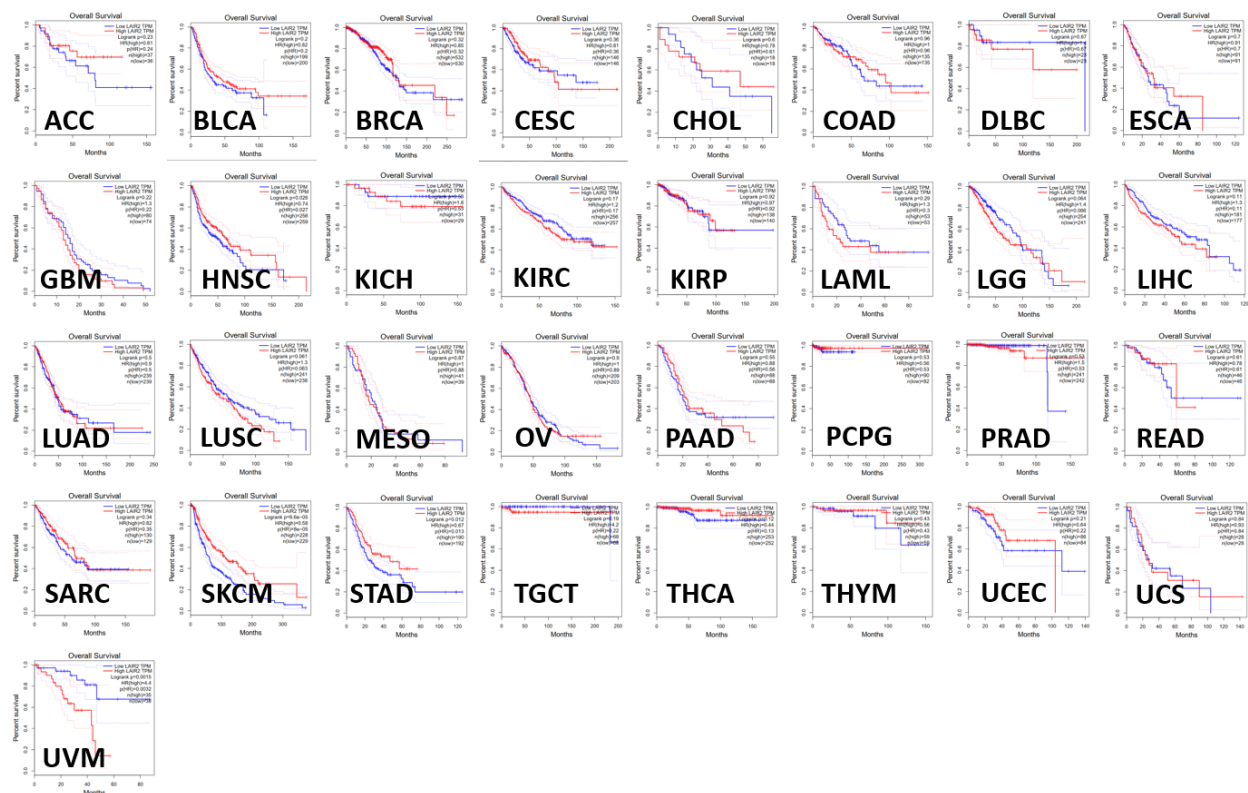
**Figure 3: Analysis of TCGA Data Sets for Expression of Markers in Tumor (T) and Normal (N) Tissues**



Normal expression uses GTex data. Yellow indicates low expression and red indicated high expression based on the scale on the right side of the figure. Blue boxes highlight eight tumor types that fit criteria as potential indications for NC410.

Further investigation revealed improved overall survival (OS) in several tumor types relative to increased expression levels of LAIR-2 (Figure 4). These data suggest patients with these tumor types may be responsive to NC410 therapy.

**Figure 4: Analysis of Overall Survival for Multiple Tumor Types Based on LAIR-2 Expression**



Overall survival was assessed for 33 cancer types from TCGA database. Abbreviations shown are TCGA study abbreviations. Analysis of overall survival Settings used for OS analysis are group cutoff: Median (50% high; 50% low); Hazards ratio based on Cox PH model, 95% confidence interval shown as dotted line. Number (n) varies across tumor types as indicated in each graph. Graphs with green boxes show three tumor types with most significant correlation between LAIR-2 high expression and improved overall survival.

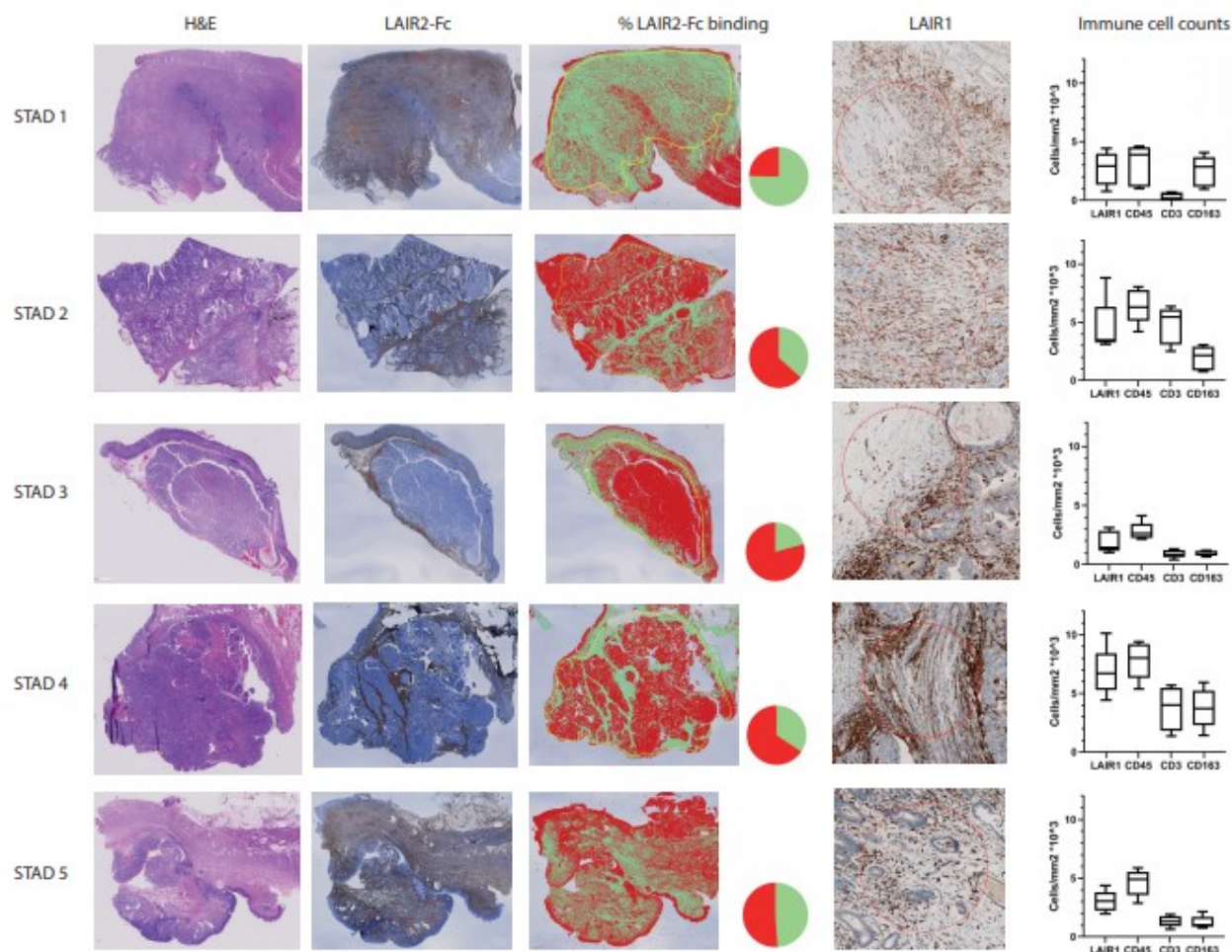
In addition to the RNA expression studies, immunohistochemical (IHC) studies were conducted to further inform identification of potential tumor types for NC410 therapy; these IHC studies were also based on criteria from the earlier in-depth nonclinical analyses of tumor types. Selection of tumor types for IHC studies utilized the following criteria:

- LAIR-1 expression in the TME
- CD163 M2-like macrophage marker, as assessed for relative increase in cancer vs normal tissues

- Analysis of several LAIR ligands, as assessed for overexpression in the TME in comparison to normal tissues
- Expression of HMGB1, as assessed by increased RNA levels in tumor versus normal tissues.

To assess these markers, IHC analysis, including hematoxylin and eosin (H&E) and trichrome staining, LAIR-1 expression, LAIR-2-Fc (NC410) binding and immune cell infiltration, was performed. Example of these results from the analysis of the stomach adenocarcinoma (STAD) (Figure 5).

**Figure 5: IHC staining of stomach adenocarcinoma**

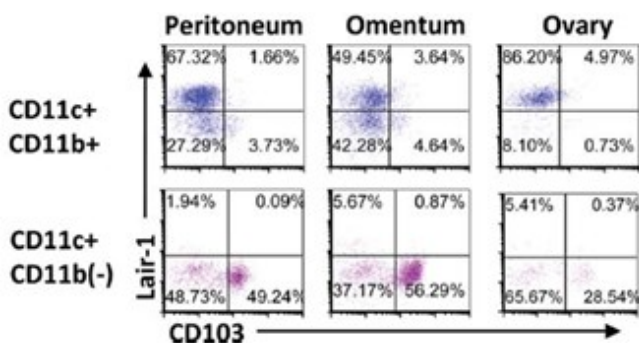


The analysis of five representative samples of stomach adenocarcinoma (STAD) is shown above. STAD tissues were analyzed by H&E staining, for LAIR-2-Fc (NC410) binding and by immuno staining of LAIR-1, CD45, CD3 and CD163 positive cells. For LAIR-2-Fc binding, brown staining indicates the binding of LAIR2-Fc, and blue staining is hematoxylin counterstaining indicating no binding by LAIR2-Fc. LAIR-2 Fc positive (green) and negative areas (red) were quantified as demonstrated in the associated piecharts. Five regions of interest (ROI) with a diameter of 600  $\mu$ m were randomly chosen in the LAIR-2 Fc positive area for immune cell quantification. One of the ROIs was magnified to show the LAIR-1 staining. The graph shows the quantification of immune cells. The cell

counts of LAIR-1<sup>+</sup>, CD45<sup>+</sup>, CD3<sup>+</sup> and CD163<sup>+</sup> cells within the five ROI were quantified and calculated as  $\times 10^3/\text{mm}^2$ .

In addition to these described parameters, it is also known that LAIR-1 is highly restricted to the hematopoietic compartment and is only expressed on immune cells. Specifically, it has been observed that LAIR-1 expression is associated with suppressive immune cell populations in some cancers. A suppressive, but not stimulatory dendritic cell (DC) subpopulation, as well as suppressive macrophages express LAIR-1 in both mouse and human ovarian cancers (Figure 6), indicating that blockade of LAIR-1 in ovarian cancer should reverse immune suppression (Flies et al., 2016).

**Figure 6: LAIR-1 is expressed on suppressive DCs in a spontaneous model of ovarian cancer**



In the MISIR Tg spontaneous model of ovarian cancer, LAIR-1 is expressed on CD11c+CD11b+ suppressive DCs at primary and metastatic sites of disease. LAIR-1 is not expressed on the stimulatory DCs (Flies et al., 2016).

The CLIA validation with IHC staining studies are ongoing, but early data support further investigation of tumor types identified in the initial analyses. Therefore, to further elucidate the effects of NC410, 5 different tumor types have been selected for investigation in Phase 1b and 2 and will include HNSCC, NSCLC (adenocarcinoma), CRC, gastric, and cervical cancers. A Simon 2-stage design will be used with a stopping rule to allow early termination of a cohort at the end of Stage 1 if insufficient response is observed, and enough subjects will be enrolled to predict possible target responses ( $\geq 25\%$ ) worthy of cohort expansion and potential for further evaluation in future studies. Finally, additional tumor types may be added (by amendment) based on emerging data for clinical investigation.

### 1.3.4 Rationale for Efficacy Endpoints

Efficacy endpoints of this study are secondary and include objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and progression-free survival (PFS) by investigator assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and modified RECIST (mRECIST).

RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen with immunotherapy (Chiou & Burotto, 2015). Immunotherapeutic agents may produce antitumor



effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents. Therefore, RECIST v1.1 will be used with the following adaptations:

If radiologic imaging shows initial progressive disease, then tumor assessment should be repeated at least 4 weeks but no later than 6 weeks later to confirm disease progression with the option of continuing treatment while awaiting radiologic confirmation of progression.

In subjects who have initial evidence of radiological progression but are clinically stable as defined below, it is at the discretion of the treating physician whether to continue a subject on study drug until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of disease progression if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms indicating disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

If repeat imaging shows < 20% tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial disease progression), and stable/improved nontarget disease (if identified as cause for initial disease progression), then treatment may be continued or resumed. If repeat imaging confirms disease progression due to any of the scenarios listed below, then subjects will be discontinued from study therapy. However, if a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks but no later than 6 weeks apart demonstrating progression) per mRECIST, but the subject is achieving a clinically meaningful benefit, then an exception to continue treatment may be considered after consultation with the medical monitor. Clinically stable subjects at the confirmatory scan should also have no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (non-worsening disease progression) to continue study treatment.

In determining whether the tumor burden has increased or decreased, site study teams should consider all target lesions as well as nontarget lesions (refer to RECIST v1.1 guidelines).

**Scenarios where disease progression is confirmed at repeat imaging include the following:**

- Tumor burden remains  $\geq 20\%$  and at least 5 mm absolute increase compared with nadir
- Nontarget disease resulting in initial disease progression is worse (qualitative)
- New lesion resulting in initial disease progression is worse (qualitative)

- Additional new lesion(s) are found since the last evaluation

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression considers the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy but with subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of disease progression.

## **1.4 Summary of Clinical Experience**

The phase 1 study of NC410, first in human study, has been initiated since 2020 with a 3+3 dose escalation design. Thus far the study has been conducted up to cohort 5 (NC410 at 60mg Q2W dosing) with no safety signals. PK, PD and biomarkers data suggested that NC410 is pharmacologically active and in addition, there are a few subjects with stable disease control.

## **1.5 Research Hypotheses**

NC410 will be adequately tolerated following administration in multiple ascending doses to subjects with refractory solid tumors and that such administration may result in clinical benefit.

# **2 OBJECTIVES AND ENDPOINTS**

## **2.1 Objectives**

### **2.1.1 Primary Objectives**

- 1) To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of NC410
- 2) To define an MTD or PAD of NC410

### **2.1.2 Secondary Objectives**

- 1) To evaluate the PK profile of NC410
- 2) To assess preliminary efficacy of NC410

### **2.1.3 Exploratory Objectives**

- 1) To assess the immunogenicity of NC410
- 2) To explore biomarkers that may predict the pharmacologic activity of NC410
- 3) To characterize the effect of NC410 on markers of immunity

## **2.2 Study Endpoints**

### **2.2.1 Primary Endpoints**

- 1) Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). **Note:** Toxicity grading per NCI CTCAE v5.0.
- 2) The MTD or PAD of NC410 will be defined in subjects with advanced or metastatic solid tumors

### **2.2.2 Secondary Endpoints**

- 1) Assessment of PK of NC410 include individual NC410 concentrations in serum and identification of PK parameters.
- 2) Assessment of antitumor activity/efficacy include objective response (OR) and DCR based on RECIST v1.1, DoR, PFS, and overall survival (OS) as per RECIST v1.1 and mRECIST v1.1

### **2.2.3 Exploratory Endpoints**

- 1) Immunogenicity, defined as the occurrence of ADA to NC410 will be determined.
- 2) Biomarker effects of NC410 in peripheral blood and tumor tissue will be assessed, including but not limited to the following:
  - Whole blood immune cell population profiling/immune-phenotyping.
  - Serum markers of inflammation or immune modulation (cytokine levels).
  - Tumor biopsy analyses to evaluate the TME within tumor tissue and characterize immune cell infiltrate at baseline and after treatment, to correlate expression levels with efficacy. The expression of additional biomarkers will also be assessed.

## **3 STUDY DESIGN**

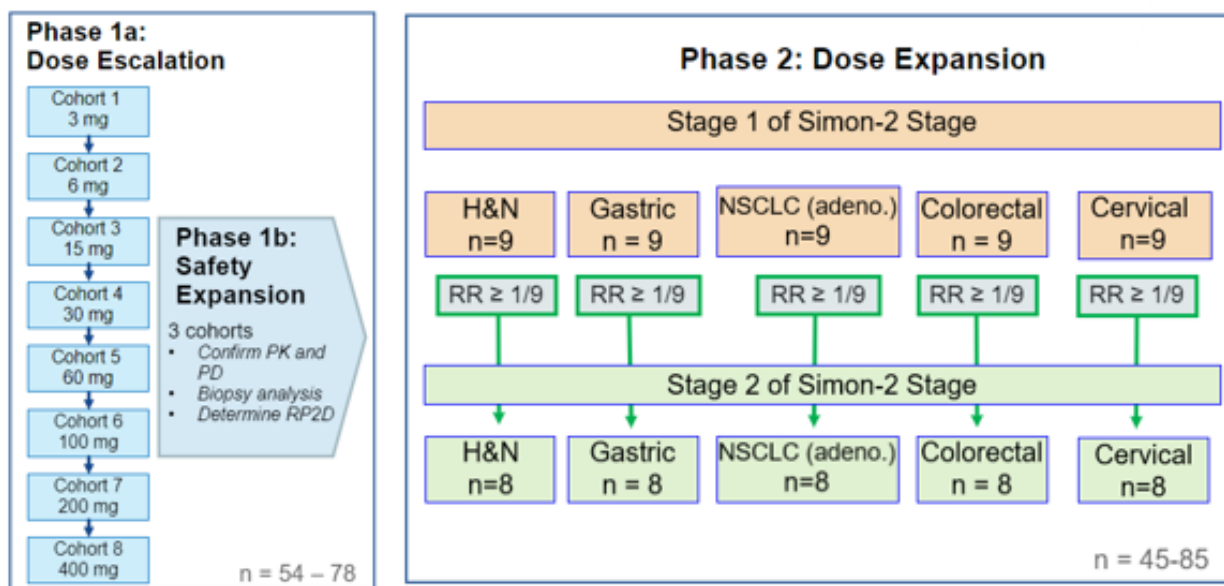
### **3.1 Description of the Study**

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety and tolerability, define the MTD or PAD, and to assess the preliminary efficacy of NC410 in subjects with advanced or metastatic solid tumors. Subjects will receive NC410 on Day 1 of each cycle. Phase 1 of the study will begin with 14-day cycles; however, alternate dose administration schedules may also be explored depending on PK, PD, biomarker, safety results, and feedback from investigators. The study will be conducted in 2 parts:

- Phase 1 – Dose Escalation (Phase 1a) and Safety Expansion (Phase 1b) will determine the MTD and/or the PAD, defined as a dose that provides a maximal biochemical effect, or an increase in biomarkers of immune activity. It will also define the optimal dose administration schedule and the maximum number of tolerated doses (MNTD).
- Phase 2 – Dose Expansion will evaluate the recommended dose and administration schedule determined in Phase 1 in subjects with advanced or metastatic HNSCC, NSCLC (adenocarcinoma), CRC, gastric, and cervical cancers or other tumor type as identified with emerging data.



**Figure 7: Study Design**



RR: Response Rate (ORR) per RECIST v1.1

### 3.1.1 Phase 1

#### 3.1.1.1 Phase 1a - Dose Escalation

In Phase 1a, subjects with advanced or metastatic solid tumors who progressed after treatment with available therapies that are known to confer clinical benefit, who are intolerant to treatment, or refuse standard treatment will be enrolled. A 3 + 3 design will be utilized to determine the MTD or PAD of NC410.

A minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (3 mg; starting dose). The first 3 evaluable subjects within a cohort will be observed for a DLT observation period of 28 days before the next cohort begins enrollment. Only one subject can be dosed on the first day of dosing for each cohort (additional subjects can begin dosing in ≥48 hours). The dose will be escalated if 0 of the first 3 evaluable subjects enrolled has a DLT. If 1 of the first 3 evaluable subjects enrolled has a DLT, then the cohort will be expanded to include 3 additional evaluable subjects, and if no DLT occurs in the additional 3 subjects, then the dose will be escalated. If a DLT occurs in one-third or more of the expanded cohort, then the MTD will be deemed to be exceeded and the previous dose level will be considered the MTD. Intermediate dose levels below the MTD may be explored pending safety review. If only 3 subjects were treated at the MTD or PAD, then a minimum of 3 additional evaluable subjects will be enrolled at this dose before it is administered in Phase 2 of the study.

If starting dose exceeds the MTD, the sponsor and investigators will consider dosing NC410 at a lower dose, and/or investigate 3 mg at alternate dose schedules, based on available safety, PK, PD, and biomarker data. If an alternate schedule is determined to be safe, re-escalation of NC410 will proceed according to Table 1.

Throughout the treatment period, if  $> 33\%$  of subjects (a minimum of 6 subjects) experience a  $\geq$  Grade 3 toxicity related to study drug after completing  $\geq 4$  cycles, then dose administration will be stopped, and the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects. Subjects who drop out for reasons other than a DLT (e.g., events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity) during the 28-day DLT observation period will be considered non-evaluable and will be replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted; however, once the RP2D and schedule has been determined, ongoing subjects in Phase 1 may be permitted to escalate to the RP2D only with approval of the medical monitor assuming the subject has not experienced  $\geq$  Grade 3 toxicity in previous treatment cycles. The cohorts and dose levels are shown in Table 1.

**Table 1: NC410 Dose Levels and Cohorts**

Cohort	Dose of NC410
1 (Starting dose)	3.0 mg
2	6.0 mg
3	15 mg
4	30 mg
5	60 mg
6	100 mg
7	200 mg
8	400 mg

### 3.1.1.2 Phase 1b – Safety Expansion

To evaluate additional PD activity of NC410 and confirm the preliminary safety of the dose escalation cohorts, Phase 1 of the study will include safety expansion cohorts (denoted as Phase 1b) evaluating doses and schedules equivalent to or lower than the highest dose levels determined to be safe and/or doses determined to be pharmacologically active. Fixed doses of NC410 (equivalent to or less than the MTD/PAD determined during dose escalation), may also be explored during the safety expansion. All doses and schedules explored during the safety expansion will depend on PK, PD, biomarker, and safety results.

Approximately 30 evaluable subjects will be enrolled in the Phase 1b safety expansion, with each cohort enrolling up to 10 additional subjects; screening and on treatment biopsies will be required.

If  $< 3$  of 9 evaluable subjects experience a DLT, the cohort will be deemed safe. If  $> 1$  safety expansion cohort is deemed safe, then a recommended dose and schedule will be determined in conjunction with the investigators and sponsor based on all available safety, PK, PD, and biomarker results.

The safety expansion cohorts may be conducted in parallel to Phase 2 and may be limited by the sponsor to subjects with specific tumor types to achieve a balance across cohorts.

### **3.1.2 Phase 2 – Dose Expansion**

Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the RP2D of NC410 in subjects with advanced or metastatic HNSCC, NSCLC (adenocarcinoma), CRC, gastric, and cervical cancers or other tumor identified based upon emerging data. Each cohort will be comprised of an individual tumor type. Biopsies at screening and on treatment will be required of all enrolled Phase 2 subjects.

A Simon 2-stage design will be utilized with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. During Stage 1, 9 evaluable subjects will be enrolled in each cohort; if no responses are observed within the cohort then the cohort will be discontinued. If at least 1 response is observed, 8 additional evaluable subjects will be enrolled in the cohort (Stage 2), for at least 17 evaluable subjects per cohort.

Subjects will continue to receive NC410 at the RP2D and schedule until protocol-defined withdrawal criteria are met. Continuous evaluation of toxicity events will be performed throughout enrollment in Phase 2 of the study. If the cumulative incidence of DLTs occurs in  $\geq 33\%$  of subjects after 6 subjects have been observed for at least 28 days, further enrollment may be interrupted until the sponsor has determined the appropriate course of action. All AEs, regardless of the time of occurrence on study may be considered in determining the appropriate dose, schedule, and MNTD.

Toxicity will continue to be monitored throughout the treatment period. If  $> 33\%$  of subjects (minimum of 6 subjects) experience a  $\geq$  Grade 3 toxicity related to study drug after completing  $\geq 4$  cycles, then the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

## **3.2 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.

## **3.3 Number of Subjects**

### **3.3.1 Planned Number of Subjects**

Up to approximately 163 evaluable subjects may be enrolled in this study.

- Phase 1a Dose Escalation – Approximately 24–48 evaluable subjects

- Phase 1b Safety Expansion – Up to 30 additional evaluable subjects
- Phase 2 Dose Expansion – Up to 85 evaluable subjects (up to 45 in stage 1)

### **3.3.2 Replacement of Subjects**

Subjects may be replaced for any of the following reasons:

- In Phase 1, any subject who 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)
- In Phase 1b and Phase 2, a subject who has not met the biopsy requirements for the study (i.e. pre- and on-treatment samples) may not be eligible to enroll.
- Subject does not meet the eligibility requirements of the study (accidental enrollment)

### **3.4 Duration of Treatment and Subject Participation**

After signing the informed consent form (ICF), screening assessments may be completed over a period of up to 30 days. Subjects will continue to receive NC410 until disease progression, withdraw of consent, or intolerable toxicity (whichever comes first). After completing 12 months of treatment, if the subject is deriving benefit from NC410 and has not met any of the protocol-defined conditions for withdrawal or discontinuation, the subject will be followed by the PI per standard of care. Subjects approved to continue treatment will remain on the dose level assigned at the time of enrollment (unless otherwise approved for dose modification by the medical monitor). Safety reporting will continue through end of treatment to completion of the safety follow-up period. If the subject discontinues treatment with NC410, then the treatment period will end, and the subject will enter the follow-up period (see [Section 6.4](#)).

### **3.5 Overall Study Duration**

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have completed the last study follow-up visit or have discontinued study drug and have completed applicable follow-up assessments.

The end of the study may be declared when no more than 5 subjects remain on study drug 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 drug and be seen by the investigator per standard of care. The investigator will be expected to monitor for and report any serious AEs (SAEs) and pregnancies, as detailed in [Sections 8.3](#) and [8.5](#). The remaining subjects will be considered on study until a discontinuation criterion is met and written notification is provided to the sponsor.

### **3.6 Study Termination**

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) 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 IECs, 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

A subject who meets all the following criteria may be included in the study:

- 1) Men and women aged 18 or older.
- 2) Willingness to provide written informed consent for the study.
- 3) ECOG performance status 0 to 1.
- 4) Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
  - a. **Phase 1a:** Subjects with advanced or metastatic tumors including but not limited to: head and neck squamous cell carcinoma, non-small cell lung cancer, ovarian cancer, cervical cancer, endometrial cancer, gastric cancer (including stomach, esophageal, and gastroesophageal junction), hepatocellular carcinoma (HCC), melanoma, pancreatic cancer, Merkel cell carcinoma, colorectal cancer (CRC), metastatic castrate resistant prostate cancer (CRPC), renal cell carcinoma (RCC), triple negative breast cancer (TNBC), urothelial carcinoma, and other tumors considered likely to respond to immune checkpoint inhibitors.
  - b. **Phase 1b and Phase 2:** Subjects with HNSCC, NSCLC (adenocarcinoma), CRC, gastric, and cervical cancers. These proposed indications may change based on emerging data and at the discretion of the Sponsor.
- 5) Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment. **Note:** There is no limit to the number of prior treatment regimens.
- 6) Presence of measurable disease based on RECIST v1.1.

**Note:** Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.
- 7) Willingness to undergo pretreatment and on-treatment tumor biopsies (core or excisional).

**Note:** For Phase 1a, pretreatment tumor biopsies are optional. Biopsies are required for all Phase 1b and Phase 2 subjects.

**Note:** For Phase 1b, archival biopsy sample will be accepted. For Phase 2, fresh biopsy sample is preferred.

**Note:** An archival biopsy obtained within 6 months of screening for other purposes (i.e., not an NC410-01 study procedure) before signing consent may be utilized.

- 8) Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy and are not postmenopausal, defined as  $\geq 12$  months of amenorrhea) **and** non-sterilized male subjects must agree to take appropriate precautions to avoid pregnancy or fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug.

**Note:** Females of child-bearing potential must have a negative serum pregnancy test at screening.

## 4.2 Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

- 1) Inability to comprehend or unwilling to sign the ICF.
- 2) Laboratory and medical history parameters not within the protocol-defined range.
  - a. Absolute neutrophil count  $< 1.5 \times 10^9/L$ .
  - b. Platelets  $< 100 \times 10^9/L$ .
  - c. Hemoglobin  $< 9$  g/dL or  $< 5.6$  mmol/L.
  - d. Serum creatinine  $> 1.5 \times$  institutional upper limit of normal (ULN) *or* calculated creatinine clearance  $< 50$  mL/min (using Cockcroft-Gault formula)
  - e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\geq 2.5 \times$  ULN.  
**Note:** Subjects with documented liver metastases may enroll with ALT, AST, and alkaline phosphatase  $\leq 5 \times$  ULN. Subjects with documented bone metastases may enroll with alkaline phosphatase  $\leq 5 \times$  ULN.
  - f. Total bilirubin  $\geq 1.5 \times$  ULN  
**Note:** Subjects with documented Gilbert's syndrome with elevated baseline total bilirubin  $\leq 3.0$  mg/dL may be enrolled.
  - g. International normalized ratio (INR)/prothrombin time (PT)  $> 1.5 \times$  ULN and Activated partial thromboplastin time (aPTT)  $> 1.5 \times$  ULN; applies only to subjects who do not receive therapeutic anticoagulation; subjects receiving therapeutic anticoagulation should be on a stable dose.
- 3) Transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 7 days before the first administration of study drug.

- 4) Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study drug:
- a.  $\leq 14$  days for chemotherapy, targeted small molecule therapy, hormonal therapy or radiation therapy. Subjects must not have had radiation pneumonitis because of a treatment. A 1-week washout is permitted for palliative radiation to non–central nervous system (CNS) disease provided recovery is adequate.  
**Note:** Bisphosphonates and denosumab are permitted medications; continuation of hormonal therapy is allowed for CRPC patients.
  - b.  $\leq 28$  days for prior immunotherapy or persistence of active cellular therapy (e.g., chimeric antigen receptor T cell therapy; other cellular therapies must be discussed with the medical monitor to determine eligibility).
  - c.  $\leq 28$  days for a prior mAb used for anticancer therapy except for denosumab.
  - d.  $\leq 7$  days for immune-suppressive–based treatment for any reason.  
**Note:** Use of inhaled or topical steroids or corticosteroid use for radiographic procedures is permitted.  
**Note:** The use of corticosteroids equivalent to prednisone  $\leq 10\text{mg/day}$  is allowed.
  - e.  $\leq 28$  days or 5 half-lives,  $t_{1/2}$ , (whichever is longer) before the first dose for all other investigational study drugs or devices.
  - f.  $\leq 14$  days for a COVID-19 vaccine. **Note:** For 2-dose COVID-19 vaccines, subjects must wait at least 14-days after 2nd dose administration.
- 5) Has not recovered to  $\leq$  Grade 1 from toxic effects of prior therapy (including prior immunotherapy and radiation therapy) and/or complications from prior surgical intervention before starting therapy.
- Note:** Subjects with stable chronic conditions ( $\leq$  Grade 2) not expected to resolve (such as neuropathy and alopecia) are exceptions and may enroll.
- Note:** Subjects with a history of any grade immune-related ocular AE (e.g., episcleritis, scleritis, uveitis) will be excluded.
- Note:** Subjects with a history of a Grade 3 or higher irAE from prior immunotherapies are excluded from the Phase 1a dose-escalation portion of the study.
- 6) Receipt of a live vaccine within 30 days of planned start of study therapy.
- 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.
- 7) Active autoimmune disease that required systemic treatment in the past (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).
- Note:** Subjects with hyperthyroidism or hypothyroidism, who have not required systemic treatment for an autoimmune disease for at least 2 years and are stable on thyroid hormone replacement are allowed to participate in the study.

**Note:** Replacement and symptomatic therapies (e.g. insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) are not considered a form of systemic immune suppressive therapy and are allowed.

- 8) Known active CNS metastases and/or carcinomatous meningitis.

**Note:** Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 7 days before the first dose of study drug.

- 9) 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.

- 10) Evidence of active, noninfectious pneumonitis or history of interstitial lung disease.

- 11) Subjects with screening QTc interval > 470 milliseconds (corrected by Fridericia) are excluded.

- 12) Uncontrolled systemic fungal, bacterial, viral, or other infection despite appropriate anti-infection treatment.

- 13) Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV), unless it is considered to be cured.

**Note:** Subjects with no prior history of hepatitis B infection who have been vaccinated against hepatitis B and who have a positive antibody against hepatitis B surface antigen test as the only evidence of prior exposure may participate in the study.

**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 prior to assessing subject eligibility.

**Note:** Subjects with prior hepatitis B virus [HBV] infection must have HBV viral load [VL] < 100 IU/mL before study enrollment and must be treated according to local standards; hepatitis C virus [HCV] infection must have, before study enrollment, no detectable VL and must be treated according to local standards.

- 14) Known history of HIV (HIV 1 or HIV 2 antibodies).

- 15) Known allergy or reaction to any component of study drug or formulation components.

- 16) Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 90 days after the last dose of study treatment.

- 17) Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.



## **5 TREATMENT**

### **5.1 Treatment Assignment**

#### **5.1.1 Subject Numbering and Treatment Assignment**

All subjects will sign an ICF and be assigned a unique 7-digit subject number with the first 3 digits serving as the site number. The subject numbering will be managed by the Sponsor/CRO

Investigative sites must complete all applicable CRFs for subjects consented to the trial, even if the subject is not treated with study drug.

Dose level and cohort assignment will occur at time of subject enrollment and as indicated by the sponsor or designee. Dose level and cohort assignment will be maintained within the CRF per the CRF completion guidelines and managed by the Sponsor/CRO

All subjects will be assigned to a cohort to receive NC410; 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 Study Drug**

#### **5.2.1 Description and Administration**

The study drug (NC410) is in frozen liquid form formulated for iv infusion, over a minimum of 30 minutes on Day 1 of each cycle (if the infusion is interrupted for any non-clinical reason, sites must notify the medical monitor). The drug product is provided in two concentrations. The 20 mg/mL configuration has 320 mg/vial in 16.0 mLs of deliverable volume whereas the 1 mg/mL configuration has 1 mg/vial in 16.0 mLs of deliverable volume. The drug can be diluted as low as 0.04 mg/mL; additional information can be found in the NC410 IB. The infusion site should not be used for blood sampling.

#### **5.2.2 Supply Packaging and Labeling**

Study drug will be supplied as 16mL aqueous solution in 20 mL glass vials with either 20 mg/mL or 1 mg/mL of NC410. 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 study drug.

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

#### **5.2.3 Storage**

Study drug must be stored in a freezer (-20°C to -50°C), 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 Pharmacy Manual contains additional information regarding storage of study drug.

#### **5.2.4 Accountability**

Detailed information such as requirements for accountability and disposal of study drug can be located within the pharmacy manual, which will be provided separately.

### **5.3 Treatment Compliance**

Compliance with study drug 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.

### **5.4 Treatment Interruptions and Adjustments**

#### **5.4.1 Dose Modifications**

Selections and modifications to the study drug are planned for dose-escalation cohorts (after consultation with the medical monitor). Dose interruptions and modifications also may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts (see [Section 5.4.2](#)). The occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects. Intrasubject dose escalation is not permitted; however, once the RP2D has been determined, ongoing subjects in Phase 1 may be permitted to dose escalate to the RP2D only with medical monitor approval assuming the subject has not experienced  $\geq$  Grade 3 toxicity in previous treatment cycles.

#### **5.4.2 Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose**

The evaluation period for DLTs will begin on Cycle 1 Day 1 and will continue up to 28 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 2, except for events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD/PAD of study drug, decisions will be made based on events that are observed from the first day of study drug administration through and including the 28-day DLT period. A lower MTD may subsequently be determined based on relevant toxicities that become evident after the 28-day DLT period.

**Table 2: Definition of Dose-Limiting Toxicity**

Nonhematologic toxicity
<p>Any <math>\geq</math> Grade 3 nonhematologic toxicity <b>EXCEPT</b> the following:</p> <ul style="list-style-type: none"> <li>• Transient (<math>\leq 72</math> hours) abnormal laboratory values without associated clinically significant signs or symptoms.</li> <li>• An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.</li> <li>• Asymptomatic changes in lipid profiles.</li> <li>• Asymptomatic changes in amylase and lipase.</li> </ul> <p>Single or non-fasting elevations in blood glucose <b>Note:</b> Any non-hematologic toxicity <math>\geq</math> Grade 3 should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.</p>
Hematologic toxicity
<ul style="list-style-type: none"> <li>• Grade 3 thrombocytopenia with clinically significant bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent medical intervention).</li> <li>• Grade 4 thrombocytopenia.</li> <li>• <math>\geq</math> Grade 3 febrile neutropenia (absolute neutrophil count <math>&lt; 1.0 \times 10^9/L</math> and fever <math>&gt; 38.3^\circ C</math>).</li> <li>• Grade 4 neutropenia that does not recover to <math>\leq</math> Grade 2 in <math>\leq 3</math> days after interrupting study drug.</li> <li>• Grade 4 anemia not explained by underlying disease or some other concomitant disorder.</li> </ul>
Immune-related toxicity
<ul style="list-style-type: none"> <li>• <math>\geq</math> Grade 2 ocular irAEs</li> <li>• Grade 3 irAEs that do not improve to baseline or at least Grade 1 in <math>&lt; 5</math> days with appropriate care or with corticosteroid therapy</li> <li>• Grade 4 irAEs regardless of duration.</li> </ul>

General
<ul style="list-style-type: none"> <li>• Inability to receive the planned number of doses within the 28-day DLT period due to toxicity, regardless of grade, will be considered a DLT.</li> <li>• Combined elevations in serum ALT &gt;3 times the upper limit of normal (ULN) <b>and</b> bilirubin &gt;2 ULN in the absence of alkaline phosphatase (ALP) elevation (&lt;2 ULN) <ul style="list-style-type: none"> <li>○ 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.</li> </ul> </li> <li>• Any death not clearly due to the underlying disease or extraneous causes.</li> </ul>
MTD
<ul style="list-style-type: none"> <li>• In Phase 1 of the study, the MTD will be defined as 1 dose level below that at which <math>\geq</math> one-third of subjects in a cohort have DLTs.</li> <li>• In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of DLTs occurs in &gt; 33% of subjects after 6 subjects have been observed for at least 28 days, then further enrollment may be interrupted, and the investigators and sponsor will meet and reassess the MTD. All AEs, regardless of the time of occurrence on study, may be considered in determining the appropriate dose, schedule, and MNTD.</li> </ul>
MNTD
<ul style="list-style-type: none"> <li>• Throughout the treatment period, if &gt; 33% of subjects (minimum of 6 subjects) experience a <math>\geq</math> Grade 3 toxicity related to study drug after completing <math>\geq</math> 4 cycles, then dose administration will be stopped, and the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.</li> </ul>

### **5.4.3 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.

### **5.4.4 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.

### **5.4.5 Procedures for Cohort Review and Dose Escalation**

Telephone conferences will be scheduled by the sponsor, or sponsor's delegate, with study investigators to review cohort-specific data and overall safety data, to agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

### **5.4.6 Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

Treatment with study drug may be delayed allowing for resolution of toxicity. 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 toxicities that occur outside of the 28-day DLT period, the treating investigator should contact the medical monitor to discuss the case of any subject whose treatment has been delayed for more than 4 weeks (28 days) before restarting treatment with study drug.

Instructions for dose modifications and interruptions are outlined in Table 3. Individual decisions regarding dose interruptions and reductions should be made using appropriate clinical judgment in consultation with the medical monitor, considering relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation, or transient ( $\leq 72$  hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules. Dose interruptions/delays are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks (28 days) of the scheduled interruption/delay, unless otherwise discussed with the medical monitor. The reason for interruption/delay should be documented in the subject's study record.

**Table 3: Rules for Interruption and Restarting of Study Drug**

NCI CTCAE v.5.0 Grade/Severity	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
1-2 (mild-moderate)	Continue treatment at the discretion of the investigator.	N/A	N/A
3 (severe)	Toxicity resolves to Grade 0-1.	Reduce by 1 dose level. <sup>a</sup>	Toxicity does not resolve within 4 weeks (28 days) of last dose, except by approval of the medical monitor. <i>or</i> Second occurrence of previously resolved Grade 3 AE.
4 (life-threatening)	Permanently discontinue.	N/A	Permanently discontinue.

Note: Permanently discontinue for any severe or Grade 3 AE that recurs or any life-threatening event.

<sup>a</sup> No more than 2 dose reductions of study drug are permitted (see Table 1). Subjects should be permanently discontinued from study drug if they have AEs requiring more than 2 dose reductions of study drug.

#### 5.4.7 Definition, Procedures, and Supportive Care Guidelines for Immune-Related Adverse Events

NC410 is an immune modulator, and it is possible that irAEs (both nonserious and serious) similar to those described with approved immunotherapies may occur. Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure ***after all other etiologies have been ruled out.*** Immune-related AEs may be expected based on the nature of NC410, its mechanism of action, and based on reported experience with other immunotherapies. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Suspected irAEs should be discussed with the medical monitor when possible.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 4. Detailed supportive care guidelines for specific irAEs can be found in Brahmer et al. (Brahmer et al., 2018). For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

**Table 4: Supportive Care Guidelines for Subjects Exhibiting Immune-Related Adverse Events**

<b>NCI CTCAE v.5.0 Grade/Severity</b>	<b>Supportive Care</b>
Grade 1 (mild)	<ul style="list-style-type: none"> <li>• Monitor symptoms and provide symptomatic treatment.</li> </ul>
Grade 2 (moderate)	<ul style="list-style-type: none"> <li>• Monitor symptoms and provide symptomatic treatment.</li> <li>• Consider consultation with specialists as necessary.</li> <li>• Consider systemic corticosteroids per institutional standard of care.</li> </ul>
Grade 3-4 (severe–life-threatening)	<ul style="list-style-type: none"> <li>• Monitor symptoms and provide symptomatic treatment.</li> <li>• Consider consultation with specialists as necessary.</li> <li>• Administer corticosteroids per institutional standard of care.</li> <li>• More potent immunosuppressive therapies should be considered for events not responding to systemic steroids after discussing with the medical monitor.</li> <li>• Study drug should be permanently discontinued for clinically significant or severe irAEs or for events where steroid course cannot be tapered below 7.5 mg/day prednisone or equivalent to manage symptoms.</li> </ul>

#### **5.4.8 Management of Infusion Reactions**

Table 5 shows treatment guidelines for subjects who experience an infusion reaction associated with 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.

**Table 5: Infusion Reaction Treatment Guidelines**

<b>NCI CTCAE v5.0 Grade/Severity</b>	<b>Treatment</b>	<b>Premedication at Subsequent Dose Administration</b>
<b>Grade 1:</b> Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None.
<b>Grade 2:</b> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for $\leq 24$ hours.	<p>Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following:</p> <ul style="list-style-type: none"> <li>• IV fluids</li> <li>• Antihistamines</li> <li>• NSAIDs</li> <li>• Acetaminophen</li> <li>• Narcotics</li> </ul> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p> <p>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be interrupted until symptoms resolve, and the subject should be premedicated for the next scheduled dose.</p> <p>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.</p>	<p>Subject may be premedicated 1.5 h (<math>\pm 30</math> min) prior to infusion with the following:</p> <ul style="list-style-type: none"> <li>• Diphenhydramine 50 mg orally (or equivalent dose of antihistamine).</li> <li>• Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).</li> </ul>



NCI CTCAE v5.0 Grade/Severity	Treatment	Premedication at Subsequent Dose Administration
<p><b>Grade 3:</b> 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).</p> <p><i>or</i></p> <p><b>Grade 4:</b> Life-threatening; pressor or ventilatory support indicated.</p>	<p>Stop infusion. Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> <li>• IV fluids</li> <li>• Antihistamines</li> <li>• NSAIDs</li> <li>• Acetaminophen</li> <li>• Narcotics</li> <li>• Oxygen</li> <li>• Pressors</li> <li>• Corticosteroids</li> <li>• Epinephrine</li> </ul> <p>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. Subject is permanently discontinued from further study drug administration.</p>	<p>No subsequent dose.</p>

#### **5.4.9 Criteria for Permanent Discontinuation of Study Drug**

The occurrence of an unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study drug and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Symptomatic Grade 4 or a life-threatening AE
- $\geq$  Grade 2 ocular irAE
- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures, or is considered to not be in the subject's best interest.
- Persistent AE requiring a delay of study drug beyond 4 weeks (28 days), unless the delay has been approved by the medical monitor.

#### **5.4.10 Treatment After Initial Evidence of Radiologic Disease Progression**

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and may manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. As a result, scans showing progressive disease should be repeated within 4-6 weeks to rule out pseudoprogression at the discretion of the PI.

If radiologic imaging shows disease progression, then subjects have the option to continue treatment while awaiting radiographic confirmation of progression as outlined in Section 7.6.1.

### **5.5 Withdrawal of Subjects from Study Drug**

#### **5.5.1 Withdrawal Criteria**

A subject may choose to withdraw from the study at any time or be withdrawn from the study by the investigator or sponsor, if the subject is noncompliant with the study requirements. Subjects may also be withdrawn at the discretion of the US FDA or health authorities. 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 study drug for the following reasons:

- The subject becomes pregnant
- Consent is withdrawn
- Further participation would be injurious to the subject's health or well being
- The subject is lost to follow-up
- Toxicity ([Section 5.4.9](#)). Subjects with unacceptable toxicities must be withdrawn from study drug but will continue to be followed during the safety follow-up visits as specified in [Section 6.4](#)

- The study is terminated by the IRB or regulatory authority
- The study is terminated by the sponsor

A subject may be discontinued from study drug as follows:

- Confirmed radiographic progression of disease per mRECIST v1.1.
- If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 4), then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

### **5.5.2 Withdrawal Procedures**

If the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study, and the end-of-treatment (EOT) visit should be conducted. Reasonable efforts should be made to have the subject complete the safety follow-up. These visits are described in [Section 6.4](#). The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study:

- The study site monitor and medical monitor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF
- The EOT visit should be performed
- The date of the EOT visit should be recorded in the eCRF
- Subjects must be followed for safety until the time of the follow-up visit or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest

If the subject discontinues study drug and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study drug but continuing in the follow-up period of the study for safety/efficacy assessments.

## **5.6 Concomitant Medications**

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study drug and 90 days after the last dose of study drug will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 90 days after the last dose of study drug should be recorded for SAEs as defined in [Section 8.3](#). Concomitant treatments/procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

### 5.6.1 Permitted Medications

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. All concomitant medications will be recorded on the eCRF, including all prescription, over-the-counter, herbal supplements, and iv medications and fluids. If changes occur during the study period, documentation of drug regimen, frequency, route, and date may also be included on the eCRF. **Note:** The use of bisphosphonates and denosumab are permitted in this study; concurrent hormonal therapy is allowed for CRPC patients.

### 5.6.2 Restricted Medications

Use of systemic glucocorticoids is restricted to prophylaxis for contrast allergies for radiographic procedures, or to modulate symptoms or treat an AE of suspected immunologic etiology. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.

**Note:** Non-systemic steroids are allowed (e.g., inhaled, intraocular, intranasal, transdermal, and topical steroids are allowed). A short course of steroids (prednisone or equivalent)  $\leq 10$  mg/day may be permitted with medical monitor approval.

Acetaminophen and NSAIDs (e.g., ibuprofen) may be used. Due to the risk of liver injury with the use of high doses of acetaminophen, subjects should be advised to stay within the recommended daily dose of acetaminophen.

### 5.6.3 Prohibited Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (see [Section 4.2](#)) are not allowed during the ongoing 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.

**Subjects are prohibited from receiving the following therapies during the screening and treatment periods of this study:**

- Any anticancer medications, including chemotherapy or biologic therapy other than the study drug.
- Any immunological-based treatment for any reason from screening through follow-up visit.

**Note:** Completed adjuvant therapy (e.g., vaccines) with medical monitor approval.

**Note:** Inhaled or topical steroids and systemic steroids at doses  $\leq 10$  mg/day prednisone or equivalents are allowed.

**Note:** Immune suppressants are allowed for treatment of immune toxicities as described in [Section 5.4.7](#) and Brahmer et al. ([Brahmer et al., 2018](#)).

**Note:** Allergy shots may be permitted after consultation with the medical monitor.

- Investigational agents other than the study drug from screening through the follow-up visits.
- Concomitant radiation therapy.

**Note:** Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the medical monitor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days before the first dose of study drug **and** while participating in the study.

**Note:** Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid (oral) 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.

- COVID-19 vaccine within 14 days prior to receiving the first dose of study drug **and** during the 28-day DLT period.

**Note:** For 2-dose COVID-19 vaccines, subjects must wait at least 14-days after 2<sup>nd</sup> vaccine dose administration.

- COVID-19 treatments/interventions including but not limited to: remdesivir, dexamethasone, convalescent plasma, supplemental oxygen, etc.

**Note:** Sites should manage COVID-19 testing as per institutional policies. In the case where the site is notified of a subject testing positive for COVID-19, investigators should contact the study Medical Monitor immediately for further guidance. Subjects who have mild or asymptomatic COVID-19 infection could stay in the study, however, subjects with severe infection needing oxygen, and other interventions including but not limited to remdesivir, dexamethasone, and convalescent plasma should discontinue study treatment. Subjects who withdraw from study treatment due to COVID-19 should be followed for safety monitoring and be encouraged to complete the End of Treatment and Safety Follow-up visits per protocol.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the investigator deems to be medically necessary. The exclusion criteria describe other medications that are prohibited in this study.

## 6 SCHEDULE OF STUDY PROCEDURES

**Table 6: Schedule of Assessments**

Visit Day	Protocol Section	Screening	Treatment <sup>a,c</sup>					Post-Treatment <sup>b</sup>		
			All Cycles	Cycles 1 & 5			Every 8/12 weeks	EOT	Safety Follow-Up 1	Safety Follow-Up 2
			Day 1	Day 2	Day 3	Day 8	Disease Status			
Evaluation/Window (Range)		Day - 30 to - 1	± 3 days (after Cycle 1)			± 1 day	± 7 days		30 days (+ 7 days)	90 days (+ 7 days)
<b>ADMINISTRATIVE PROCEDURES</b>										
Informed consent	7.1	X								
Eligibility (I/E) criteria	4	X								
Demographics	7.2	X								
Cancer History and Diagnosis	7.2	X								
Medical History <sup>d</sup>	7.2	X								
Prior/concomitant meds <sup>e</sup>	7.3						X			
Poststudy anticancer therapy and Survival status	7.4							X	X	X
<b>CLINICAL PROCEDURES/ASSESSMENTS</b>										
Administer NC410	5.2.1		X							
Comprehensive PE <sup>f</sup>	7.5.2.1	X						X		
Targeted physical assessment <sup>f</sup>	7.5.2.2		X			X		X		
Vital signs and weight	7.5.3	X	X <sup>g</sup>			X		X		
ECOG performance	7.5.2.1	X	X			X		X		
12-lead ECG <sup>h</sup> (Table 11)	7.5.4	X <sup>i</sup>	X <sup>j</sup>					X <sup>i</sup>		
AE assessment	7.5.1						X			
Laboratory assessments <sup>k</sup> (Table 7 and Table 8)	7.5.5	X	X			X		X		
PK/PD assessments (Table 9 and Table 10)	7.7 and 7.8		X	X	X	X		X		
Tumor Biopsy <sup>l</sup>	7.8	X	X					X		
<b>EFFICACY MEASUREMENTS</b>										
Radiologic assessments	7.6.1.1	X <sup>m</sup>					X <sup>n</sup>	X <sup>o</sup>		X <sup>o</sup>

- a Treatment cycles will begin every 14 days ( $\pm 3$  days after Cycle 1). Alternate dosing schedules may also be explored based on emerging data.
- b Mandatory safety follow-up should be conducted approximately 30 days and 90 days after EOT visit (or after last dose of study drug if EOT was not performed). Safety follow-up should be performed before the initiation of a new systemic anticancer treatment, regardless if it occurs before or during the safety follow-up period. Safety follow-up may be performed by phone.
- c Visit at Day 8 is required for all subjects at Cycles 1 and 5. Visits on Days 2 and 3 are applicable for Phase 1 subjects only.
- d Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.
- e Any prior medication received up to 30 days before the first dose of study drug and 90 days after the last dose of study drug will be recorded in the eCRF. Please also refer to sections 5.6.2 and 5.6.3 for details on prohibited and restricted medications.
- f 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 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. The screening physical examination should also include a measurement of height. The 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 or Medical History (if applicable at Screening).
- g During Cycle 1, subjects will be required to stay at the study site for safety observation for 4 hours post-infusion. Vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose, at the end of infusion, and every 60 minutes  $\pm 10$  minutes for 4 hours post end of infusion. For all subsequent cycles (with the exception of Cycle 5), subjects will be required to be observed for 1 hour post end of infusion or per PI discretion, if indicated. Vitals signs will be assessed pre-dose, at the end of infusion ( $+10$  minutes), and thereafter at the PI's discretion. Subjects will also be assessed for the onset of acute AEs.
- h All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection.
- i A single 12-lead ECG is required at screening and EOT.
- j A single 12-lead ECG should be performed on Day 1 of Cycles 1 and 5 at the following timepoints: pre-infusion ( $-30$  minutes) and post-infusion ( $+30$  minutes). Additional ECGs should be performed per PI discretion if any clinically significant abnormal findings are noted or as indicated.
- k If a central line is used for study drug infusion, collect blood samples via peripheral blood draw to prevent sample contamination.
- l For Phase 1a, tumor biopsies are optional. Biopsies are required for all Phase 1b and Phase 2 subjects. Biopsies will be collected at Screening and at Cycle 3 (prior to Cycle 4 dose). An optional EOT biopsy will be collected for subjects who consent for EOT biopsy at time of ICF.
- m The initial tumor imaging will be performed within 30 days before the first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days before the first dose of study drug. The same imaging technique should be used for a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
- n On-study imaging will be performed at Week 8 and then every 8 weeks ( $56 \text{ days} \pm 7 \text{ days}$ ) for the first 6 months and then every 12 weeks ( $84 \text{ days} \pm 7 \text{ days}$ ) thereafter. For subjects who continue treatment beyond 12 months, imaging should be performed per standard of care and per PI discretion. Imaging should follow calendar days and should NOT be adjusted for delays in cycle starts. If imaging shows disease progression, then another imaging assessment should be performed 4 to 6 weeks later to confirm progression per mRECIST.
- o If scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation (EOT) is not mandatory. For subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (i.e., date of discontinuation  $\pm 4$ -week window). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status every 8 weeks ( $56 \text{ days} \pm 7 \text{ days}$ ) for the first 6 months (from first dose) and then every 12 weeks ( $84 \text{ days} \pm 7 \text{ days}$ ) by radiographic imaging until 1) withdrawal of consent, 2) the start of new systemic anticancer therapy, 3) documented disease progression, 4) death, or 5) the end of the study, whichever occurs first.

**Table 7: Schedule of Local Laboratory Assessments**

Visit Day	Protocol Section	Screening <sup>a</sup>	Treatment				Post-Treatment
			C1, and C5		All Other Odd Numbered Cycles (C3, C7, C9, etc.)	Even Numbered Cycles (C4, C6, C8, C10, etc.)	EOT
			D1 <sup>b,c</sup>	D8	D1 <sup>c</sup>	D1 <sup>c</sup>	
Evaluation/Window (Range)		Day - 30 to - 1	Pre-infusion	± 1 day	- 3 days	- 3 days	
Comprehensive serum chemistries <sup>d</sup>	7.5.5	X	X	X	X	X	X
Hematology with differential <sup>e</sup>	7.5.5	X	X	X	X	X	X
Coagulation panel <sup>f</sup>	7.5.5	X	X	X	X		X
Total Hemolytic Complement Test (CH50)	7.5.5		X		X		X
Urinalysis <sup>g</sup>	7.5.5	X	X	X	X		X
Endocrine function tests <sup>h</sup>	7.5.5	X	X	X	X		X
Hepatitis B and C <sup>i</sup>	7.5.5.2	X					
Serum pregnancy test (childbearing females only) <sup>j</sup>	7.5.5.1	X <sup>k</sup>					X
Urine pregnancy test (childbearing females only) <sup>l</sup>	7.5.5.1		X <sup>m</sup>		X <sup>m</sup>	X <sup>m</sup>	

a Serum chemistry, hematology, coagulation, urinalysis, and endocrine function tests must be performed during screening period.

b Laboratory samples on Cycle 1 Day 1 must be performed before study drug administration. Safety lab results should be reviewed by the investigator designee and found to be acceptable prior to the administration of study drug.

c After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours before study drug administration. Safety lab results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

d Chemistry required analytes in Table 8.

e Hematology required analytes in Table 8.

f Coagulation panel required analytes in Table 8. Per PI discretion, coagulation panel can be discontinued after Cycle 5 unless directly related to AE/SAE or as indicated.

g Urinalysis required analytes in Table 8. Urine dipstick – if positive, perform microscopic urinalysis. Per PI discretion, urinalysis can be discontinued after Cycle 5 unless directly related to AE/SAE or as indicated.

h Endocrine function tests required analytes in Table 8.

i Hepatitis testing required analytes in Table 8.

j Serum pregnancy testing obtained from females of child bearing potential only.

k The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study drug.

l If positive, confirm results with serum pregnancy test.

m For women of child-bearing potential only, Day 1 urine pregnancy must be performed and resulted before study drug administration.



**Table 8: Local Laboratory Tests: Required Analytes**

Serum Chemistries	Hematology	Urinalysis	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphorus Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Amylase Lipase	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Mean corpuscular volume  Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils  <b>Absolute values must be provided for the following WBC differential laboratory results:</b> White blood cells Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA* HCV antibody HCV-RNA*  <b>*Note:</b> If HCV/HBV antibody or antigen tests are positive, reflex testing (HCV RNA and/or HBV DNA tests) should be performed to confirm results prior to assessing subject eligibility.	PT aPTT INR
		<b>Complement Assay</b>	<b>Endocrine Function Tests</b>	<b>Pregnancy Testing</b>
		Total Complement Test (CH50)	Thyroid-stimulating hormone Free thyroxine (Free T4) Total triiodothyronine (Total T3)/ Free triiodothyronine (Free T3) <sup>b</sup>	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.

WBC = white blood cell.

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

a Urine pregnancy tests are only required if medically indicated or a country-specific requirement.

b Based on site standard

**Table 9: Schedule of Pharmacokinetic and Anti-Drug Antibody Sampling**

Study Visit	Phase 1	Phase 2	Assessment	Timing of Sample Collection
Cycle 1 Day 1	X	X	PK and ADA	• Pre-infusion
	X		PK	• Post-infusion (+ 10 min) • 2 h ( $\pm$ 30 min) post-infusion • 4 h ( $\pm$ 30 min) post-infusion
Cycle 1 Day 2	X		PK	• 24 h ( $\pm$ 60 min) post-infusion
Cycle 1 Day 3	X		PK	• 48 h ( $\pm$ 60 min) post-infusion
Cycle 1 Day 8	X		PK	• Untimed PK sample
Cycle 2 Day 1	X		PK	• Pre-infusion
Cycle 3 Day 1	X	X	PK and ADA	
	X	X	PK and ADA	
Cycle 5 Day 1	X		PK	• Post-infusion (+ 10 min) • 2 h ( $\pm$ 30 min) post-infusion • 4 h ( $\pm$ 30 min) post-infusion
Cycle 5 Day 2	X		PK	• 24 h ( $\pm$ 60 min) post-infusion
Cycle 5 Day 3	X		PK	• 48 h ( $\pm$ 60 min) post-infusion
Cycle 5 Day 8	X		PK	• Untimed PK sample
Cycle 6 Day 1	X		PK	• Pre-infusion
Day 1 of Cycles 7, 9, 11, 17, and 23	X	X	PK and ADA	• Pre-infusion
End of Treatment	X	X	ADA	• Untimed ADA sample

**Table 10: Schedule of Pharmacodynamic (Biomarker) Sampling**

Biomarker Assessment	Study Visit	Phase 1	Phase 2	Timing of Sample
Whole blood immunophenotyping	Cycle 1 Day 1	X	X	• Pre-infusion
	Cycle 1 Day 3	X		• Anytime
	Cycle 3 Day 1 Cycle 5 Day 1 Cycle 7 Day 1 Cycle 11 Day 1 Cycle 23 Day 1	X	X	• Pre-infusion
Serum correlative sample for cytokine levels	Day 1 of Cycles 1, 5	X	X	<ul style="list-style-type: none"> <li>• Pre-infusion</li> <li>• Post-infusion <ul style="list-style-type: none"> <li>○ ≤ 60 min post-infusion</li> <li>○ With 2h PK</li> <li>○ With 4h PK</li> </ul> </li> </ul>
	Day 2 of Cycles 1 and 5	X		• Anytime
	Day 1 of Cycle 11	X	X	<ul style="list-style-type: none"> <li>• Pre-infusion</li> <li>• Post-infusion</li> </ul>
Biopsies <sup>a</sup>	Screening Cycle 3 <sup>b</sup> EOT	X	X	• Anytime
Plasma ctDNA	Day 1 of Cycle 1	X	X	• Pre-infusion

a Tumor biopsies are optional for Phase 1a. Screening (pre-treatment) and Cycle 3 (on-treatment) biopsies are mandatory for Phase 1b and Phase 2. EOT biopsies are optional for Phase 1 and 2.

b Cycle 3 (± 1 week). Biopsy must be completed prior to 1<sup>st</sup> on-treatment scan (~ Cycle 4) and subsequent dose.

## 6.1 Screening

Screening is the interval between signing the ICF and the day the subject is enrolled in the study (e.g., Cycle 1 Day 1). Screening should not exceed approximately 30 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.

## 6.2 Treatment

The treatment period begins on the day the subject receives the first dose of study drug (Cycle 1 Day 1) through the point at which the investigator determines that the subject will be permanently discontinued from study drug. Cycle 1 Day 1 must take place within approximately 30 days after the subject has signed the ICF.

Subjects will have regularly scheduled study visits on Day 1 of every cycle ( $\pm 3$  days after Cycle 1). Additional visits will be required on Day 2 and 3 (Phase 1 only) and Day 8 (all subjects) of Cycles 1 and 5. During study visits, the subject will have clinical and laboratory assessments as outlined in Table 6 and Table 7. At certain study visits as indicated in [Section 7.7](#) and [Section 7.8](#), subjects will have PK, PD, and biomarker samples obtained (see Table 9 and Table 10). Toxicities will be monitored continuously and will be graded using the NCI CTCAE v5.0 criteria.

**During Cycle 1 subjects will be required to stay at the study site for safety observation for 4 hours post end of infusion.** On Day 1 of all subsequent cycles (with the exception of Cycle 5) subjects will be required to be observed for a minimum of 1 hour post end of infusion or per PI discretion if indicated. It is recommended that the subject does not leave the site for any reason during the safety observation period. During the safety observation period, subjects will be assessed for the onset of acute AEs.

After completing 12 months of treatment, if the subject is deriving benefit from NC410 and has not met any of the protocol-defined conditions for withdrawal or discontinuation, the subject will be followed by the PI per standard of care. Subjects approved to continue treatment will remain on the dose level assigned at the time of enrollment (unless otherwise approved for dose

modification by the medical monitor). Safety reporting will continue through end of treatment to completion of the safety follow-up period.

### **6.3 End of Treatment**

When the subject permanently discontinues study drug, 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 return for the follow-up visit(s).

### **6.4 Follow-up**

#### **6.4.1 Safety Follow-up**

The safety follow-up period is the interval between the EOT visit and the scheduled follow-ups, which should occur 30 days (+ 7 days) and 90 days (+ 7 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). AEs and SAEs must be reported up until at least 90 days after the last dose of study drug, the date of the last safety follow-up, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. The safety follow-up must be performed before any new systemic anticancer therapy is started regardless of whether it occurs before or during the safety follow-up period; it can, in fact, be done on the same day provided it is done before the start of the new systemic anticancer therapy (e.g. prior to dosing).

#### **6.4.2 Disease Status Follow-up**

Subjects who discontinue study drug for a reason **other than** disease progression will move into the disease status follow-up period and should continue to be assessed every 8 weeks (56 days  $\pm$  7 days) for the first 6 months and then every 12 weeks (84 days  $\pm$  7 days) thereafter or per standard of care, by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the earliest of the following:

- Withdrawal of consent
- The start of a new systemic anticancer therapy
- Documented disease progression
- Death
- End of the study

### **6.5 End of Study**

The end of the study will occur when all subjects have completed the last study follow-up visit or have discontinued study drug and have completed applicable follow-up assessments.

Additionally, subjects will be considered as having completed the study if they meet any of the following criteria:

- Subject dies and a date of death is available
- Subject is known to have died; however, the date of death cannot be determined

- Consent is withdrawn for any further contact to this study (Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded)
- The study is terminated by the sponsor
- The study is terminated by the IRB or local health authority

## **6.6      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.

# **7           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. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study.

## **7.1      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/IEC. 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.

## **7.2      Demography and Medical History**

### **7.2.1      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 relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

### **7.2.2      Disease Characteristics and Treatment History**

A disease-targeted medical and medication history will be collected at screening. Details regarding the subject's malignancy under study including date of diagnosis, initial and current cancer stage, primary tumor histology, and prior treatments including systemic, radiation, and

surgical procedures will be recorded. For subjects with cancer types commonly-associated with Human Papillomavirus (HPV), HPV status will be collected.

### **7.3 Prior and Concomitant Medications and Procedures**

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received, or procedure performed within 30 days before the first dose of study drug and up to the end of the follow-up phase of the study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. 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.

### **7.4 Poststudy Anticancer Therapy and Survival Status**

The investigator or qualified designee will review all new systemic anticancer therapy initiated after the last dose of study drug. The subject's survival status and death details (if applicable) will also be collected.

**Note:** If a subject initiates a new systemic anticancer therapy within 30 to 90 days after the last dose of study drug, the 30-day or 90-day safety follow-up should occur **before** the first dose of the new systemic anticancer therapy.

### **7.5 Safety Assessments**

#### **7.5.1 Adverse Events**

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of 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 8.1](#).

#### **7.5.2 Physical Examinations**

##### **7.5.2.1 Comprehensive Physical Examination**

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. ECOG performance status should be assessed.

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. The screening physical examination should also include a measurement of height.

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

#### **7.5.2.2 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.

#### **7.5.3 Vital Signs and Weight**

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

On Cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be collected pre-dose, at end of infusion (+10 minutes), and every 60 minutes ( $\pm 10$  minutes) thereafter for 4 hours post end of infusion.

On Day 1 of all subsequent cycles, vital signs will be assessed pre-dose, at end of infusion (+10 minutes), and thereafter at the PI's discretion.

It is recommended that the subject does not leave the site for any reason during the safety observation period. Subjects will also be assessed for the onset of acute AEs

Weight will also 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.

#### **7.5.4 Electrocardiograms**

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes of a blood collection. ECG assessments will be done as shown in Table 11.

A single 12-lead ECG should be performed at Screening and EOT for all subjects.

On Day 1 of Cycles 1 and 5, ECG's will be collected at the following timepoints: pre-infusion (-30 minutes) and post-infusion (+30 minutes). Additional ECGs should be performed per PI discretion if any clinically significant abnormal findings are noted or as indicated.

The automated 12-lead ECGs readings will be interpreted by the investigator, or qualified designee at the site to be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on a locally analyzed ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the medical monitor, as appropriate. Clinically significant abnormal findings before signing consent should be recorded as medical history. Clinically significant abnormal findings after signing consent should be recorded as an AE. For any subjects with clinically significant



abnormalities, ECGs may be conducted more frequently than the protocol-required timepoints per PI discretion.

**Table 11: Timing of Electrocardiograms**

Study Visit	Timing of Sample		
	Any Time	Pre-infusion (-30 minutes)	Post-infusion (+30 minutes)
Screening	X		
C1D1		X	X
C5D1		X	X
EOT	X		

### 7.5.5 Laboratory Assessments

A laboratory local to the study site and subject will perform all clinical laboratory assessments for safety (i.e., blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results into the eCRF and select the laboratory name so that the laboratory normal ranges will populate. All local laboratory assessments should be performed using standard procedures on the days indicated in Table 6 and Table 7. Table 8 lists the specific laboratory analytes required for each test. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Serum chemistry, hematology, coagulation, urinalysis, and endocrine function tests must be performed during the screening period.

Laboratory samples collected on Cycle 1 Day 1 must be performed before study drug administration. Cycle 1 Day 1 safety lab results should be reviewed by the investigator or qualified designee and found to be acceptable prior to study drug administration.

After Cycle 1, pre-infusion laboratory procedures can be conducted up to 72 hours before study drug administration, and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

#### 7.5.5.1 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 7, as medically indicated, or per country-specific requirement. 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.

### 7.5.5.2 Hepatitis Screening Tests

Hepatitis screening assessments will be performed at the screening visit (Table 7) 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. Additional tests may be performed if clinically indicated.

## 7.6 Efficacy Assessments

### 7.6.1 Modified RECIST v1.1 Assessment of Disease

Modified RECIST will be applied by the site as the primary measure for assessment of tumor response and as a basis for protocol guidelines related to disease status (e.g., discontinuation of study therapy). As noted in [Section 1.3.4](#), RECIST v1.1 has been adapted to account for the unique tumor responses seen with immunotherapy ([Wolchok et al., 2009](#)).

If radiologic imaging shows progressive disease, then tumor assessments should be repeated at a minimum of 4 weeks, but no later than 6 weeks later to confirm progression, with the option of continuing treatment while awaiting radiologic confirmation of progression. **Table 12** provides instructions on how to proceed with treatment based on the subject's clinical status once the initial scan showing radiologic evidence of progression is observed.

Subjects may receive treatment while waiting for confirmation of progression if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory findings) consistent with disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease

Absence of progressive tumor at critical anatomic sites (such as spinal cord compression) requiring urgent alternative medical intervention

**Table 12: Imaging and Treatment After First Radiographic Evidence of Progressive Disease**

	Clinically Stable		Clinically Unstable	
	Tumor Imaging	Treatment	Tumor Imaging	Treatment
First radiologic evidence of progression	Repeat imaging 4-6 weeks to confirm progression	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging	Repeat tumor imaging 4-6 weeks to confirm progression per physician discretion only	Discontinue treatment
Repeat scan confirms progression	No additional tumor imaging required	Discontinue treatment	No additional tumor imaging required	N/A

Repeat scan shows SD, PR, or CR	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion
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SD = stable disease; PR = partial response; CR = complete response.

As noted above, if disease progression is observed, then the study site may elect to continue treatment and repeat imaging at a minimum of 4 weeks, but no later than 6 weeks later, to assess tumor response or confirm progression per mRECIST.

In determining whether or not the tumor burden has increased or decreased, study site investigators should consider all target lesions as well as nontarget lesions. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

If radiologic progression is confirmed by subsequent scan, then the subject should be discontinued from study treatment. If radiologic progression is not confirmed, then the subject should resume or continue study treatment and have the next tumor imaging according to the protocol schedule (see Table 6). If progression is not confirmed and the subject continues on treatment, then the date of the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks, but no later than 6 weeks later) will be considered the date of disease progression.

If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks, but no later than 6 weeks apart demonstrating progression) per mRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered after consultation with the medical monitor. Clinically stable subjects at the confirmatory scan should also have no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (non-worsening disease progression) to continue study treatment.

### 7.6.1.1 Tumor Imaging

**The same imaging technique should be used for a subject throughout the study.** The baseline scan must be a contrast computed tomography (CT) or magnetic resonance imaging (MRI), except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography/CT uses higher energy and thinner slices, it may be acceptable with medical monitor approval. **Images of the chest and abdomen are required for all subjects.**

#### 7.6.1.1.1 Tumor Imaging During Screening

Initial tumor imaging must be performed within 30 days before the first dose of study drug. The site study team must review pre-study images to confirm that the subject has measurable disease per RECIST v1.1. Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. If a subject only has lesions in an area previously irradiated or subjected to locoregional therapy but has had shown measurable progression subsequent to the therapy, then the subject will be allowed to

enroll. Additionally, it is recommended that tumor lesions selected for biopsy **not** be selected as target lesions.

CT or MRI scan of the brain will be performed at screening if there are signs or symptoms suggesting that the subject has disease involvement in the CNS. An MRI of the brain will also be required at screening for all subjects with melanoma.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days before the first dose of study drug.

#### **7.6.1.1.2 Tumor Imaging During the Study**

The first imaging assessment should be performed 8 weeks after the first dose of study drug and then every 8 weeks (56 days  $\pm$  7 days) for 6 months and then every 12 weeks (84 days  $\pm$  7 days) thereafter until disease progression is determined. Subjects who remain on treatment beyond 12 months will have imaging performed per standard of care and PI discretion. Imaging assessments may be done more frequently if clinically indicated. **Imaging should not be delayed for delays in cycle starts.**

**NOTE:** If imaging is delayed, the missed scan should be conducted as soon as possible, and all subsequent scans must remain on schedule (every 8/12 weeks relative to the first dose of NC410) and should not be adjusted.

Per mRECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date that the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated.

Imaging should continue to be performed until documented disease progression, the start of new systemic anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks, but no later than 6 weeks after the first scan indicating progression in clinically stable subjects.

Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed, provided that they have met the conditions detailed in [Section 7.6.1](#). A central imaging vendor will not be used in this study.

#### **7.6.1.1.3 Imaging During Follow-Up**

If the subject discontinues study drug for reasons other than disease progression, imaging assessments should continue at the protocol-specified interval until documented disease progression, the start of a new systemic anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

If scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation (EOT) is not mandatory. For subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be repeated at the time of

treatment discontinuation (i.e., date of discontinuation  $\pm$  4-week window). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status every 8 weeks (56 days  $\pm$  7 days) for the first 6 months (from first dose) and then every 12 weeks (84 days  $\pm$  7 days) thereafter until 1) withdrawal of consent 2) the start of new systemic anticancer therapy, 3) documented disease progression, 4) death, or 5) the end of the study, whichever occurs first.

## 7.7 Pharmacokinetic Assessments

PK and ADA samples will be obtained at the visits and times indicated in Table 9. 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 study drug. After the pre-dose PK sample is drawn, subjects will begin the study drug infusion. Adjustments to the timing of blood sampling may be made based on emerging PK data. The exact date and time of each PK blood draw will be recorded in the eCRF. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

## 7.8 Biomarker and Correlative Assessments

Tumor, whole blood, and serum samples will be collected at the visits outlined in Table 10. 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 or immune 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 Laboratory Manual for the study.

### 7.8.1 Tumor Biopsies

#### 7.8.1.1 Tumor Tissue Collection Requirements

Tumor biopsy samples are **optional for the Phase 1a dose escalation** portion of the study. Tumor biopsy samples are **required for subject participation in the Phase 1b safety expansion and Phase 2** of the study.

Mandatory and optional tumor biopsies will be collected as specified below:

- **Screening (mandatory in Phase 1b Safety Expansion and Phase 2):** A baseline biopsy obtained for other purposes (i.e., not an NC410-01 procedure) may be utilized if the subject has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (Cycle 1 Day 1). **Note:** Fresh tumor biopsies should be taken from nontarget lesions when possible.

- **On-treatment (mandatory in Phase 1b Safety Expansion and Phase 2):** A second mandatory on-treatment biopsy must be obtained anytime during Cycle 3  $\pm$  1 week (prior to 1<sup>st</sup> on-treatment scan (~ Cycle 4) and subsequent dose). **Note:** On-treatment biopsies should be performed at the same site as the screening biopsy whenever possible.
- **At the End of Treatment (optional):** A third optional tumor specimen referred to as the End of Treatment (EOT) biopsy may be obtained at the time that study treatment has been discontinued.

If a subject is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the subject may still enroll in the study after consultation with the medical monitor.

**NOTE:** Details and methods for obtaining, processing, and shipping the fresh tumor biopsy samples will be provided in the Laboratory Manual for the study.

#### 7.8.1.2 Tumor Tissue Assessment

Tumor biopsy samples will be used to investigate molecular signatures associated with response or resistance to treatment with the study drug. DNA and/or RNA may be extracted from these samples to perform somatic mutation analysis, epigenetic analysis, whole exome sequencing, and genetic expression analysis. Tissue may also be examined by histology and immunohistochemistry or by exploratory methods to evaluate markers of inflammation and T-effector cell populations, growth, signaling, apoptosis, etc. that may be associated with safety, response, or resistance to treatment with the study drug.

#### 7.8.2 Whole Blood Correlative Assessment

Whole blood samples will be used for immune cell population profiling (which may include T lymphocytes, B lymphocytes, myeloid, and natural killer cells). Analysis of T cell receptor (TCR) clones may also be analyzed to detect evidence of on therapy clonal expansion. Other assays relevant to the objectives of the study, such as flow cytometry analysis of intracellular cytokines, may be performed based upon emerging data.

#### 7.8.3 Serum Pharmacodynamic Assessment

Serum samples will be evaluated to assess evidence of NC410 activity.

Serum samples will be used to examine markers of inflammation, immune modulation, and remodeling of the tumor microenvironment (which may include but are not limited to: IFN $\gamma$ , IL-2, IL-4, IL-6, and TNF $\alpha$ ) pre- and on-treatment with NC410. Other assays relevant to the objectives of the study may be performed based on emerging data.

#### 7.8.4 Timing for Serum and Whole Blood Assessments

Biomarkers will be analyzed in serum and whole blood samples collected at baseline and on the days and times as outlined in Table 10. Throughout the study, the exact date and time of the biomarker blood draws will be recorded in the eCRF along with the date and time study drug was administered in the clinic. For information regarding handling/shipping of specimens, please refer to the Laboratory Manual for the study.

## 7.9 Other Study Procedures

Not applicable.

## 8 SAFETY MONITORING AND REPORTING

### 8.1 Adverse Events

#### 8.1.1 Definitions

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. AEs 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.

A treatment-emergent adverse event (TEAE) is one that occurs from the time of the first dose of study drug through 90 days after the last dose of study drug. TEAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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).

#### 8.1.2 Reporting

AEs that begin or worsen after informed consent should be recorded on the AE form in the eCRF. **Monitoring for the occurrence of new AEs should be continued for at least 90 days after the last dose of study drug.**

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

The severity of AEs will be assessed using NCI CTCAE v5.0 Grades 1 through 4. **The NCI CTCAE v5.0 severity of Grade 5 will not be used;** AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal.

If an event is not classified by NCI CTCAE, the severity of the AE will be graded according to Table 13 to estimate the grade of severity.

**Table 13: NCI CTCAE v5.0 Grading Scale**

<b>Grade</b>	<b>Clinical Characteristics</b>
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 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.

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 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to 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 8.3.1](#)

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see [Section 8.3.2](#)).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the AE form in the eCRF and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

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.

## 8.2 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 form in the 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 8.3.1](#). A dose modification for the laboratory abnormality may be required (see [Section 5.4.6](#)) and should not contribute to the designation of a laboratory test abnormality as an SAE.

## 8.3 Serious Adverse Events

### 8.3.1 Definitions

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

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.

- Constitutes a congenital anomaly or birth defect.
- Is an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

Symptoms and clinical manifestations of disease progression can be classified as an SAE (if it meets the above criteria); however, progressive disease is not an SAE.

### 8.3.2 Reporting

**Within 24 hours of identifying an SAE, 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 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. 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 also needs to be provided the Sponsor or its designee within 24 hours of learning of the new information.

### 8.3.3 Reporting of an Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the NC410 IB, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, 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. NextCure does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

## 8.4 Emergency Unblinding of Treatment Assignment

Not applicable.

## 8.5 Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. 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 drug or within 30 days after cessation of treatment if the subject initiates new systemic anticancer therapy, 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).

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome. The baby should be evaluated for the first 8 weeks or the duration specified in local regulations, whichever is later.

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

## 8.6 Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). 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.

## 8.7 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established for this open-label study. For Phase 1, the sponsor in conjunction with the study medical monitor and CRO will conduct telephone conferences with investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation, de-escalation, and cohort expansion decisions on a regular basis. For Phase 2, a formal DMC will be organized and comprised of the following members including but not limited to: a chairperson, two non-participating physicians specializing in oncology, the study medical monitor, a non-voting biostatistician, and representatives of the Sponsor and CRO. The committee will meet on a regular basis to review safety and tolerability throughout the study. Additional information on the DMC will be detailed in the DMC Charter.

## 8.8 Immune-Related Adverse Events

Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on the nature of NC410, its mechanism of action, and reported experience with other immunotherapies. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Guidance for the assessment, diagnosis, and management of irAEs is provided in [Section 5.4.7](#). Suspected irAEs should be discussed with the medical monitor.

## 8.9 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: NCclin@nextcure.com

Email subject line should include: “**NC410-01 Product Complaint**”

Mail: NextCure, Inc.

Attn: Clinical Operations  
9000 Virginia Manor Road  
Beltsville, MD 20705 USA

## 9 STATISTICS

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 NC410. Additional details of statistical analyses will be described in the Statistical Analysis Plan (SAP).

## **9.1 Study Populations**

The full analysis set (FAS) includes all subjects enrolled in the study who received at least one full dose of NC410. This population will be used in all the summaries and analyses except for the of safety analysis set (SAS) and PK. The SAS will include all the subjects who receive any amount of study drug. The summaries and analyses of safety data will be performed on the SAS. The PK analysis set (PAS) will include all the subjects whose blood samples are collected for PK analysis. The PK data summaries and analyses will be performed on the PAS.

## **9.2 Selection of Sample Size**

A maximum of 163 eligible subjects in Phase 1 and Phase 2 (78 + 85) will be included in this study.

### **9.2.1 Sample Size for Phase 1**

The primary objective of the dose escalation part in Phase 1 of the study (Phase 1a) is to determine the MTD or PAD of NC410. A 3 + 3 study design will be used for dose escalation. A maximum of 8 dose levels will be tested. Therefore, a maximum of 48 subjects, who are evaluable for DLTs, will be included in the dose escalation phase. Subjects evaluable for DLTs are defined as the subjects who take a full dose of NC410 and then are followed up for 28 days for assessment of DLTs. Any subjects who do not meet the criteria will be replaced.

Phase 1 of the study may also include safety expansion cohorts (Phase 1b) evaluating doses and schedules equivalent to or lower than the highest dose levels determined to be safe and/or doses determined to be pharmacologically active. Each safety expansion cohort will enroll up to an additional 10 evaluable subjects (total of 30 additional subjects in the Phase 1b). If < 3 of 9 evaluable subjects experience a DLT, the cohort will be deemed safe. If more than 1 safety expansion cohort is deemed safe, then the RP2D will be determined in conjunction with the investigators and sponsor based on all available safety, PK, PD, and biomarker results.

### **9.2.2 Sample Size for Phase 2**

Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of NC410. The sample size for each tumor type will be guided by the Simon 2-stage design ([Simon, 1989](#)). Let 5% be a clinically insignificant response rate for all tumor types. During Stage 1, 9 subjects will be enrolled; if no responses are observed, then the cohort will be discontinued. If at least 1 response is observed, then 8 additional subjects will be enrolled (Stage 2), for a maximum of 17 subjects per tumor type in Phase 2. The detailed calculation is based on a 1-sided Type I error of 0.05 and power of 80% to detect a 25% response rate for each of the tumor types.

## **9.3 Level of Significance**

There is no formal hypothesis test planned for this study. A statistically significant level of 0.05 is used for calculation of CI.

## 9.4 Interim Analysis

No formal interim analysis is planned. However, the safety, PK and efficacy data will be regularly reviewed and monitored for decisions involving dose escalation in Phase 1 and continuation in Phase 2 of the study.

## 9.5 Statistical Analyses

### 9.5.1 Safety Analyses

The safety assessments include adverse events, laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis), ECG, physical examination, vital signs, ECOG performance status, and medical history. All the safety data in the SAS will be summarized and listed by phase, treatment group, and cohort.

#### 9.5.1.1 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 4.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. 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.

#### 9.5.1.2 Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 14) and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

**Table 14: Criteria for Clinically Notable Vital Sign Abnormalities**

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

### 9.5.1.3 Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. ECG results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 15). Subjects exhibiting clinically notable ECG abnormalities will be listed.

**Table 15: Criteria for Clinically Notable Electrocardiogram Abnormalities**

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

### 9.5.2 PK Analyses

The PK analyses will be based off the PAS, and PK time-concentration data will be summarized, listed, and plotted. PK parameters ( $AUC_{0-336}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $t_{1/2}$ , etc.) derived from time-concentration data will be summarized.

### 9.5.3 Efficacy Analyses

The response will be assessed by CT/MRI image during screening and every 8 weeks ( $56 \pm 7$  days) post-dosing for 6 months and then every 12 weeks ( $84 \pm 7$  days) thereafter (or per standard of care). The efficacy study endpoints include ORR, DCR, DoR, PFS, and OS. Tumor response will be determined according to RECIST v1.1. Time-to-event data (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. All the efficacy data will be summarized by phase, dose group, and cohort.

- ORR includes RECIST v1.1 complete and partial response (CR or PR). ORR with 95% exact confidence interval (CI) will be summarized by phase, dose group, and cohort.
- DCR includes RECIST v1.1 complete, partial response, and stable disease (CR, PR or stable disease lasting 24 weeks or longer). DCR with 95% exact CI will be summarized by phase, dose group, and cohort.
- DoR is defined as the duration from the first documented ORR to the first documented progressive disease or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of discontinuation from study, data cutoff for analysis, or use of other anticancer drug, DoR will be censored at the last tumor assessment date.

The DoR will only be analyzed for the subgroup of subjects with an objective response.

DoR = (progressive disease, death, or censored date) – (date of first response + 1)

- PFS is defined as from starting study treatment to the first documented progressive disease or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of discontinuation from study, data cutoff for analysis, or use of other anticancer drug, PFS will be censored at the last tumor assessment date.

$$\text{PFS} = (\text{progressive disease, death, or censored date}) - (\text{date of first dose of study drug} + 1)$$

- OS is defined as from starting study treatment to death due to any cause. For subjects who are alive will be censored at the date of last known alive (LKA).

$$\text{OS} = (\text{Death or LKA date}) - (\text{date of first dose of study drug} + 1)$$

#### **9.5.4 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 NC410.

The immunogenic potential of NC410 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.

#### **9.6 Analyses for Data Monitoring Committee**

Not applicable.

### **10 STUDY AND DATA MANAGEMENT**

#### **10.1 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).



## 10.2 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, that biological samples are handled in accordance with the NC410-01 Laboratory Manual and 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.

### 10.2.1 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.

### **10.2.2 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.

## **10.3 Study Timetable and End of Study**

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment (including telephone contact), regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see [Section 5.5.1](#)).

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.

## **10.4 Data Management**

Data management will be performed according to the study specific 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.

## **10.5 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.

## **11 ETHICAL AND REGULATORY REQUIREMENTS**

### **11.1 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.

### **11.2 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 genetic data being linked to the identity of the subject. 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.

### **11.3 Ethics and Regulatory Review**

An IRB/IEC 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 investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to the sponsor or designee before enrollment of any subject into the study.

The IRB/IEC 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/IEC 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/IEC, and PIs with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

Each PI must inform the IRB/IEC 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 completion

## **11.4 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/IEC. The ICF must be approved by the IRB/IEC 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/IEC

## **11.5 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/IEC 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/IEC see [Section 11.3](#).

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/IEC 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/IEC.

## **11.6 Audits and Inspections**

Authorized representatives of NextCure, a regulatory authority, or an IRB/IEC may perform audits or inspections at the clinical sites, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, 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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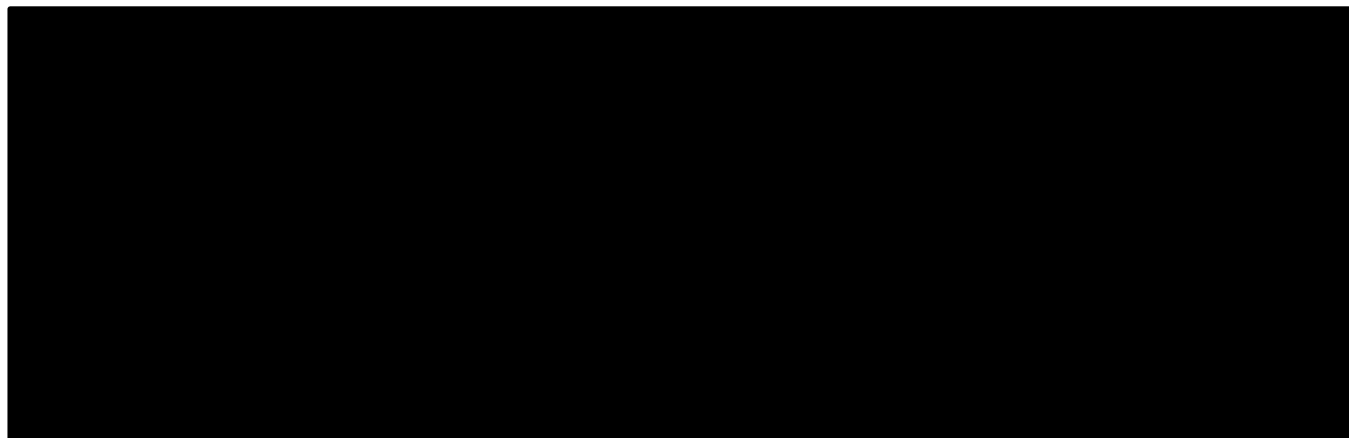
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## **Appendix 1: Signatures**

### **Sponsor Signature(s)**

#### **A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC410 in Subjects with Advanced or Metastatic Solid Tumors**

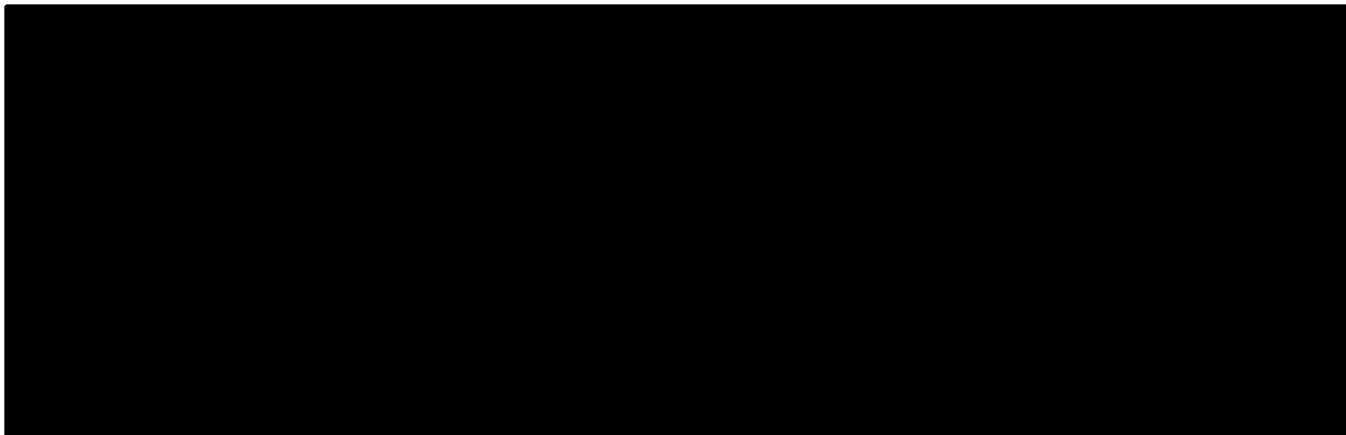
I agree to the terms of this protocol.



**Sponsor Signature(s)**

**A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of  
NC410 in Subjects with Advanced or Metastatic Solid Tumors**

I agree to the terms of this protocol.



**Signature of Principal Investigator**

**A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC410 in Subjects with Advanced or Metastatic Solid Tumors**

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/Independent Ethics Committee (IRB/IEC).

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/IEC and must be approved by the IRB/IEC 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/IEC 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) \_\_\_\_\_

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from NextCure. Investigators are cautioned that the information in this protocol may be subject to change and revision.

## Appendix 2: Additional Safety Guidance

### Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of adverse events (AEs) and serious adverse events (SAEs). Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 as provided below. The determination of severity for all other events not listed in the NCI CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 4 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc.).

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in [Section 8.3.1](#). A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

The NCI CTCAE v5.0 can be downloaded from the Cancer Treatment Evaluation Program (CTEP) ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)).

### 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 3: 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 4: Eastern Cooperative Oncology Group Performance Status**

<b>Grade</b>	<b>Eastern Cooperative Oncology Group (ECOG)</b>
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 house work, 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 5: Cockcroft-Gault Formula

Estimated creatinine clearance or glomerular filtration rate =

$$[(140 - \text{Age}) * \text{Mass (in kg)}] \div [72 * \text{Serum creatinine (in mg/dL)}]$$

If the subject is female, multiply the above by 0.85

If the subject is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated creatinine clearance.

### Calculation of Ideal Body Weight (IBW)

IBW in kg

$$\text{Males} = 50 + [2.3 \times \text{each inch over 5 ft}]$$

$$\text{or } 50 + [2.3 \text{ kg} \times (\text{each cm over } 152.4/2.54)]$$

$$\text{Females} = 45.5 + [2.3 \times \text{each inch over 5 ft}]$$

$$\text{or } 45.5 + [2.3 \text{ kg} \times (\text{each cm over } 152.4/2.54)]$$

### Calculation for Obesity

$[(\text{actual wt} - \text{IBW})/\text{IBW}] * 100\%$ . If this value is >30% then the person is obese.

Example:

Subject weight = 160. Subject ideal weight = 120

$$160 - 120 = 40$$

$$40 / 120 = 0.33$$

$$0.33 \times 100\% = 33\%$$

(Cockcroft and Gault 1976)