A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC762 in Subjects with Advanced or Metastatic Solid Tumors

Sponsor Protocol Number: NC762-01

IND Number: 145522

Investigational Product: NC762

Humanized immunoglobulin gamma 1, kappa ($IgG_1\kappa$) monoclonal antibody specific for human B7 homolog 4 (B7-H4) protein

Phase of Study: 1/2

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Protocol Synopsis

TITLE

A Phase 1/Phase 2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC762 in Subjects with Advanced or Metastatic Solid Tumors

HYPOTHESES

NC762 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 NC762
2) To define a maximum tolerated dose (MTD) or pharmacologically active dose (PAD) of NC762

Secondary Objectives

1) To evaluate the pharmacokinetic (PK) profile of NC762
2) To assess preliminary efficacy of NC762
3) To evaluate downregulation of B7-H4 expression and changes in tumor infiltrating lymphocytes after NC762 treatment.

Exploratory Objectives

1) To assess the immunogenicity of NC762
2) To explore biomarkers that may predict the pharmacologic activity of NC762

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 NC762 will be defined in subjects with advanced or metastatic solid tumors

Secondary Endpoints

1) Assessment of PK of NC762 will include individual NC762 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

3) Tumor biopsy analyses to evaluate downregulation of B7-H4 expression and changes in tumor infiltrating lymphocytes after NC762 treatment.

Exploratory Endpoints

1) Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC762, will be determined.
2) Biomarker effects of NC762 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).
   - The expression of additional histological biomarkers may 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 NC762 in subjects with advanced or metastatic solid tumors. Subjects will receive NC762 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 NC762, 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 non-small cell lung (NSCLC) (squamous cell), hepatocellular carcinoma (HCC), HER2+ breast, and ovarian cancer. 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 NC762.

A minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (0.5 mg/kg; 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 ≥ 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 NC762 at the lower dose cohorts, and/or investigate 0.5 mg/kg 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 NC762 will proceed according to the table below.

Throughout the treatment period, if > 33% of subjects (a minimum of 6 subjects) experience a ≥ Grade 3 toxicity related to study drug after completing ≥ 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, withdraw of consent, 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 ≥Grade 3 toxicity in previous treatment cycles. The cohorts and dose levels are shown in the table below.

Cohort	Dose of NC762
1 (Starting dose)	**0.5 mg/kg**
2	**1.5 mg/kg**
3	**5.0 mg/kg**
4	**10 mg/kg**
5	**20 mg/kg**

Phase 1b – Safety Expansion

To evaluate additional PD activity of NC762 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 20 evaluable subjects will be enrolled in the Phase 1b safety expansion, with each dose cohort enrolling up to 10 additional subjects. If < 3 of 10 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.

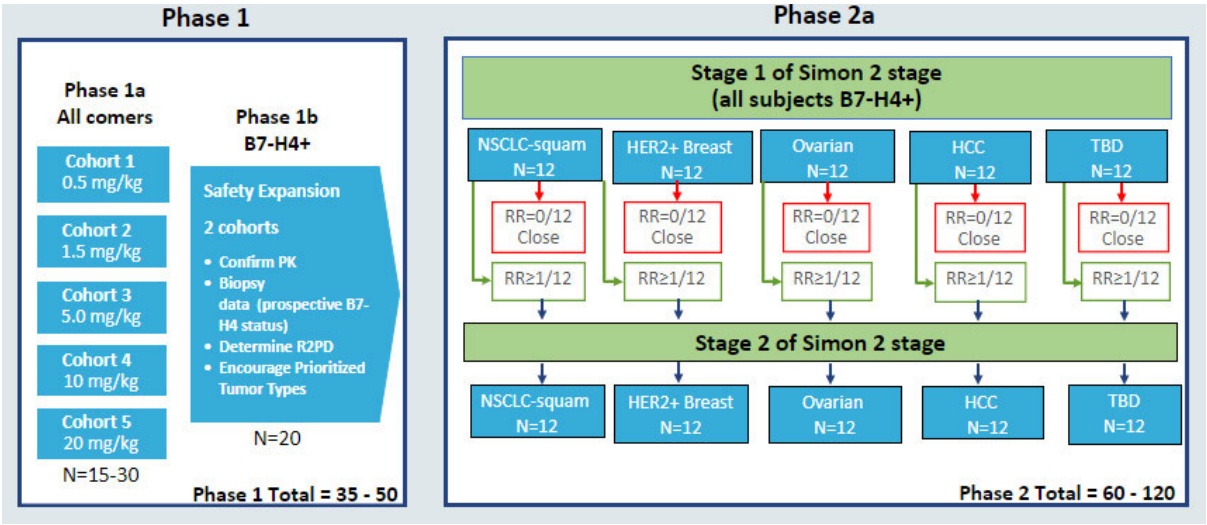
Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the RP2D of NC762 in subjects with advanced or metastatic non-small cell lung (squamous cell), hepatocellular carcinoma (HCC), HER2+ breast, and ovarian cancer. A fifth cohort may be included and will enroll patients of a tumor type pending outcomes of the Phase 1. 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, 12 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, 12 additional evaluable subjects will be enrolled in the cohort (Stage 2), for at least 24 evaluable subjects per cohort.

Subjects will continue to receive NC762 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 ≥ 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 ≥ Grade 3 toxicity related to study drug after completing ≥ 4 cycles, then the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

NC762 Study Schematic



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

NC762 will be administered by intravenous (iv) infusion, over a minimum of 30 minutes on Day 1 of each cycle. Subjects will continue to receive NC762 until disease progression or unacceptable toxicity, if the subject is deriving benefit and has not met any of the protocol-defined conditions for withdrawal. Subjects who continue to receive benefit from NC762 after completing 12 months of treatment will have the option to enroll into a separate expanded access protocol; safety assessments will be continued.

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 NC762. The sample size is not fixed and will vary based on emerging safety data at the doses studied.

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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_{max}	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_{30}	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

Abbreviation or Specialized Term	Definition
GLP	Good Laboratory Practices
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
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
ip	Intraperitoneal
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

Abbreviation or Specialized Term	Definition
ORR	Objective Response Rate
OR	Objective Response
OS	Overall Survival
PAD	Pharmacologically Active Dose
PAS	PK Analysis Set
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
$t_{½}$	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

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 NC762 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 NC762 in subjects with advanced or metastatic non-small cell lung (squamous cell), hepatocellular carcinoma (HCC), HER2+ breast, and ovarian cancer or other tumor type as identified with emerging data.

1.1 Background

1.1.1 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.

1.1.2 B7-H4 and Immunity

B7-H4 (B7 homolog 4, also known as B7x, B7S1 or VTCN1), is a member of the B7 family of costimulatory molecules (Prasad et al., 2003; Sica et al., 2003; Zang et al., 2003). It is a type-I transmembrane protein consisting of two extracellular immunoglobulin (Ig)-like domains (IgV and IgC), a transmembrane domain and a cytoplasmic domain containing two amino acids (Sica et al., 2003). B7-H4 mRNA is widely expressed in a variety of tissues (Prasad et al., 2003; Sica et al., 2003), whereas B7-H4 protein shows limited expression in most normal tissues (Choi et

al., 2003; Sica et al., 2003; Salceda et al., 2005). In contrast, B7-H4 protein is highly expressed on the surface of many types of cancer including ovarian, lung, and breast cancers (Choi et al., 2003; Salceda et al., 2005). B7-H4 expression has also been observed on tumor-associated macrophages (TAMs) in ovarian cancer (Kryczek et al., 2006). B7-H4 expression within the tumor microenvironment correlates with poor clinical outcome for multiple indications including ovarian (Kryczek et al., 2007), lung (Carvajal-Hausdorf et al., 2019), renal (Krambeck et al., 2006), melanoma (Quandt et al., 2011), prostate (Zang et al., 2007), and pancreatic (Chen et al., 2014). High expression on tumor cells but low expression on healthy cells makes B7-H4 an attractive candidate for direct targeting with low non-specific off-target toxicity.

The physiological role for B7-H4 is unclear. B7-H4 is thought to have both intrinsic and extrinsic mechanisms that lead to enhanced tumor growth. B7-H4 has been shown to increase growth and reduce apoptosis of tumor cell lines (Zhang 2017; Salceda 2005).

B7-H4 may play a role in the innate immune response. Upon injection with the bacteria *Listeria monocytogenes*, mice lacking B7-H4 have increased neutrophil recruitment resulting in lower bacterial burdens (Zhu 2009). Decreased bacterial burden was independent of the adaptive immune response, suggesting that B7-H4 modulates neutrophil function (Zhu 2009).

B7-H4 may also act as a ligand. The binding partner for B7-H4 has not been identified, however B7-H4 fusion protein has been shown to bind to activated T cells (Prasad et al., 2003; Sica et al., 2003). There are several reports that B7-H4 leads to immunosuppression of T cells. B7-H4 expression on tumor cells blocks cytokines produced by $CD8^+$ T cells (Quandt et al., 2011), and B7-H4-expressing macrophages from ovarian cancer ascites suppress T cell proliferation to a greater extent than cells lacking B7-H4 (Kryczek et al., 2006). Although published literature suggests that B7-H4 plays a role in T-cell immunosuppression, our studies have not indicated that B7-H4 expression inhibits T cell activity. B7-H4 is highly expressed in many types of cancers and limited expressed in normal tissues, which make it a great target for antibody therapy.

The interaction of B7-H4 with its receptor modulates neutrophile function. NC762 blocks the interactions between B7-H4 and its receptor which is expressed on neutrophil progenitor cells in the TME thereby blocking immunosuppression of tumor associated neutrophils (TAN). In addition, NC762 mediates tumor killing via ADCC of $B7\text{-}H4^+$ tumors. The rationale for developing NC762 for cancer is based on nonclinical models that demonstrate that the targeting of B7-H4 can improve the immune response and provide benefit in multiple oncology indications.

1.2 Overview of NC762

NC762 is a humanized immunoglobulin gamma 1, kappa ($IgG_1\kappa$) monoclonal antibody specific for human B7 homolog 4 (B7-H4) protein that is being developed for the treatment of cancer. NC762 induces anti-tumor activity may through the following mechanisms: a) binding to B7-H4 on the cell surface of tumor cells and inducing internalization to block and downregulate B7-H4 on tumor cells, b) potentially reducing neutrophil in the TME & blocking effects of B7-H4 on innate immunity, and c) directly targeting B7-H4 positive tumor cells via antibody-dependent cellular cytotoxicity (ADCC). The $IgG_1\kappa$ region of NC762 contains three-point mutations (S239D/A330L/I332E a.k.a. DLE) to allow for the enhanced binding to CD16a ($Fc\gamma RIIIa$) which increases ADCC activity in both *in vitro* and *in vivo* models.

1.2.1 Pharmacokinetics of NC762

Single-dose and repeat-dose PK of NC762 were characterized in cynomolgus monkeys. Concentrations of NC762 in serum were analyzed using a quantitative electrochemiluminescence (ECL) method developed by Meso Scale Discovery (MSD, Rockville, MD). Immunogenicity testing was also conducted in conjunction with these studies. Serum samples were screened for the presence of anti-drug antibodies (ADA) and confirmed by immune-competition with free NC762.

Repeat-dose PK of NC762 was examined in a GLP-compliant repeat-dose study in cynomolgus monkeys. Animals were administered with 0, 2, 20 or 100 mg/kg NC762 (N=5/ sex/group; 3/sex Main Group and 2/sex Recovery Group) on SD 1, 15, and 29 by 30-minute iv infusion. PK analysis showed that exposure (C_{max} and AUC) of NC762 was linearly proportional to dose level, across the range of doses that were tested. Slight accumulations were observed with the dosing. Estimates of mean clearance (Cl) were also comparable for males and females at all dose levels on SD 29. Mean Cl estimates ranged from 0.148 to 0.191 mL/h/kg from ADA negative monkeys. ADA was detected in 4 recovery animals (2 males: 1 at 20 mg/kg 1 at 100 mg/kg; and 2 females: 1 at 2 mg/kg and 1 at 100 mg/kg), which were associated with more rapid clearance of NC762. These animals were excluded when evaluating the range or average values for SD 29 (3rd dose) PK parameters such as terminal half-life and AUC, to provide a more accurate assessment of the disposition of NC762 in the absence of ADA. After 3 doses, the estimated terminal half-life of NC762 is approximately 10 days in the ADA negative monkeys. The mean serum kinetics study results are summarized in Table 1 for male and female groups.

Table 1 Mean NC762 TK Parameters on Days 1 and 29 Following Every Other Week IV Infusion of 2, 20 and 100 mg/kg to Male and Female Monkeys (GLP Study)

Dose	Gender	$T_{1/2}$ (h)	C_{max} (µg/mL)	C_{max}/Dose (kg*µg/mL/mg)	$AUC_{0\rightarrow336}$ (h*µg/mL)	$AUC_{0\rightarrow336}$/Dose (h*µg/mL/mg)	Cl (mL/h/kg)	ADA Positive
1st Dose on Day 1								
2 mg/kg	M	ND[2]	66.7	33.3	6,450	3,220	ND	ND
	F	ND	77.7	38.8	6,290	3,150	ND	ND
20 mg/kg	M	ND	618	30.9	55,000	2,750	ND	ND
	F	ND	659	329	54,300	2,720	ND	ND
100 mg/kg	M	ND	3060	30.6	290,000	2,900	ND	ND
	F	ND	3210	32.1	284,000	2,840	ND	ND
3rd Dose on Day 29[3]								
2 mg/kg	M	236	76.7	38.4	8,880	4,440	0.148	
	F	197	86.3	43.1	8,280	4,140	0.170	1
20 mg/kg	M	289	776	38.8	77,100	3,860	0.154	1
	F	187	837	41.9	83,800	4,190	0.179	
100 mg/kg	M	244	3400	34	378,000	3,780	0.191	1
	F	256	3900	39	397,000	3,970	0.184	1

[1]GLP-compliant study.
[2] Not determined.
[3]ADA positive animals were excluded for TK parameter analysis.

1.2.2 Pharmacology of NC762

The pharmacology of NC762 has been studied in *in vitro* and *in vivo* systems to support its use as an investigational drug in oncology.

In vitro binding studies found that NC762 binds to human B7-H4 with an affinity of 2.99 nM, determined using bio-layer interferometry (BLI). Flow cytometry analysis of NC762 binding to cells stably transduced with B7-H4 exhibited an EC_{50} of 1.1 nM. Human breast cancer SKBR3 cells that naturally express B7-H4 exhibited an EC_{50} for NC762 of approximately 1 nM. NC762 also binds to a CD16a-expressing cell line with high avidity. In addition, NC762 binding to SKBR3 cells induced internalization of the antibody. Antibody-dependent cell-mediated cytotoxicity (ADCC) is one of the mechanisms proposed for NC762. NC762 mediated ADCC activity against SKBR3 cells using both a reporter cell line and human PBMCs. No CDC activity was observed.

In vivo, NC762 was effective as a monotherapy in a subcutaneous (SC) human xenograft mouse model. NC762 treatment reduced tumor growth of a human melanoma cell line 624Mel expressing human B7-H4 (624Mel.hB7H4) in the presence of human PBMCs. NK cells but not T cells were involved in restricting tumor growth. Interestingly, NC762 showed activity in the absence of human PBMCs. Immunophenotyping of extracted tumors revealed that NC762 reduced mouse neutrophil in the tumor microenvironment (TME). Furthermore, NC762 with a modified IgG_1 domain that has reduced FcγR binding also showed equivalent activity suggesting that NC762 activity also has ADCC-independent mechanisms.

In vitro assays were also conducted to evaluate the risk of cytokine release syndrome (CRS). Using conditions that would have predicted the high risk of CRS for the anti-CD28 mAb TGN1412 (Findlay 2010, Stebbings 2007), NC762 did not promote cytokine release relative to a negative control (anti-RSV) (Synagis®).

For additional information, please refer to the NC762 Investigator's Brochure (IB).

1.2.3 Non-Clinical Safety and Potential Risks of NC762

The toxicology of NC762 has been studied in a variety of *in vitro* and *in vivo* systems to support its use as an investigational drug in oncology.

In the non-GLP, single dose, dose-range-finding (DRF) study, male and female monkeys (N=1/sex/group) were administered with 1, 10, 100 and 300 mg/kg NC762 by 30-min IV infusion. All animals survived up to the end of the study on SD 22. A single dose of NC762 up to 300 mg/kg was very well tolerated in both male and female monkeys. There were no NC762-related observations nor effects on food consumption, body weights, body weight change, hematology, coagulation, clinical chemistry, urinalysis, or peripheral blood leukocyte analysis (PBLA). No NC762-related macroscopic findings were seen at the terminal necropsy. In the single dose DRF study, the highest non-severely toxic dose (HNSTD) was 300 mg/kg/dose of NC762 which resulted in a C_{max} (µg/mL) of 11,400 in males and 10,700 in females; and AUC_{0-504} (hr*µg/mL) of 1,010,000 in males and 893,000 in females.

In the GLP-compliant 1-month repeat-dose study, cynomolgus monkeys were administered with 0, 2, 20 or 100 mg/kg NC762 (N=5/sex/group) on SD 1, 15, and 29 by 30-min IV infusion.

Acute toxicity was assessed on SD 31, 2 days after the 3rd dose on three animals/sex/group. Recovery necropsy (2/sex/group) was performed 10 weeks following the last dose on SD 99 to assess for reversibility, persistence, or delayed occurrence of any observed toxicities. There were no mortalities and no NC762-related effects on hematology, clinical chemistry, coagulation, urinalysis parameters, cytokine analysis, gross necropsy findings, organ weights, histopathologic examinations, clinical observations, body weight parameters, blood pressure evaluations, ophthalmology examinations, or electrocardiograph evaluations. The most notable findings were from one male monkey at the highest dose cohort, 100 mg/kg, which showed moderate to marked reduction in neutrophil counts on SD 31 (2 days after the 3rd NC762 dose, as low as 10-20% of its baseline) and on SD 37, 48, 50 and 55. On SD 99 prior to recovery necropsy, its neutrophil counts were back to normal range. Due to the decreased neutrophil counts, this animal was monitored more frequently for signs of illness, but there were no clinical or veterinary findings over the course of the study to suggest an opportunistic infection. B7-H4 was previously reported having effects on mouse neutrophil development (Zhu 2009). Due to the unique occurrence (1 out of 10 monkeys) in this animal at the highest dose level, with resolution during the non-dosing recovery period, these changes were of uncertain relation to NC762 administration.

Systemic exposure to NC762 appeared to be independent of sex. Following IV infusion administration of NC762, mean C_{max} and $AUC_{0\text{-}336hr}$ values for NC762 appeared to increase with increasing dose in an approximately dose proportional manner across the dose range on SD 1 and SD 29. Four NC762 treated monkeys developed anti-drug-antibodies (ADA), which were associated with accelerated clearance. No adverse findings were associated with ADA positivity.

A non GLP-compliant human tissue cross-reactivity (TCR) study was conducted to understand what human tissues will be bound by NC762. Membrane staining with biotinylated-NC762 was limited to hematopoietic precursor cells in the bone marrow and epithelial cells in Fallopian tube, mammary gland (ducts, glands), and placenta (amnion).

Overall, repeat IV administration of NC762 up to 100 mg/kg was well-tolerated and was not associated with any overt toxicity in cynomolgus monkeys. The highest non-severely toxic dose (HNSTD) was 100 mg/kg/dose of NC762, which corresponded with overall mean C_{max} and mean $AUC_{0\text{-}336}$ for NC762 on Day 29 of 3,650 µg/mL and 388,000 hr*µg/mL, respectively.

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 immune modulation by targeting B7-H4 expression on tumor cells and its role in creating immune-suppressive tumor microenvironment.

While immunotherapies for cancer have shown great promise, there is still an unmet medical need for additional therapies with novel approaches. Therefore, NC762 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 has considered all relevant preclinical pharmacology and toxicology data, including dose-response in human cell-based assays, and anti-tumor effects in mouse tumor models.

NC762 has been well-tolerated and repeated administration of dosages 200-fold higher (on a mg/kg basis) than the planned clinical starting dose were not associated with any adverse toxicities.

A risk assessment for NC762 was performed to support dose selection. Relevant factors for NC762 are discussed below:

The rationale for the proposed Phase 1 starting dose (SSD) of 0.5 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 syngeneic tumor models. The FDA Guidance for Industry Estimating the Maximum Safe Starting Dose (SSD) in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers was used. Since NC762 is a protein administered intravenously with a molecular weight > 100 kDa, mg/kg scaling was used. Relevant *in vivo* pharmacology data from humanized mouse model were used to select the SSD. 1 mg/kg of NC762 displayed some anti-tumor activity in the 624Mel.B7H4 tumor model. Approximately, 9 µg/mL of NC762 was detected at C_{max} in NSG mouse serum post ip injection with 1 mg/kg NC762, which resulted in a human equivalent dose (HED) of 0.5 mg/kg.

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 20 mg/kg, which is 5 folds lower than the highest non-severely toxic dose (100 mg/kg) determined by the 5-week GLP-compliant repeat-dose tox study in cynomolgus monkeys.

The following summarizes the doses recommended for FIH testing of NC762:

- Highest non-severely toxic dose (HNSTD) in monkeys = 100 mg/kg
- Dose to demonstrate minimum anti-tumor activity in NSG mouse model = 1 mg/kg, delivered ip, ~9 µg/mL NC762 in mouse serum
- Recommended starting dose = 0.5 mg/kg (5000 mL blood volume and average 80 kg were used for calculation)
- Recommended maximum dose = 20 mg/kg

1.3.2 Rationale for Dosing

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

Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the RP2D of NC762 in subjects with advanced or metastatic non-small cell lung (squamous cell), hepatocellular carcinoma (HCC), HER2+ breast, and ovarian cancer. The rationale for choosing those tumors is based on the published data as well as our own data showing B7-H4 expression is high in those tumors. A fifth cohort may be included and will enroll patients of a tumor type pending outcomes of the Phase 1.

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 ≥ 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

As this is a FIH study, no data are available in humans. There are no other ongoing studies with NC762.

1.5 Research Hypotheses

NC762 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 NC762

2) To define an MTD or PAD of NC762

2.1.2 Secondary Objectives

1) To evaluate the PK profile of NC762

2) To assess preliminary efficacy of NC762

3) To evaluate downregulation of B7-H4 expression and changes in tumor infiltrating lymphocytes after NC762 treatment.

2.1.3 Exploratory Objectives

1) To assess the immunogenicity of NC762

2) To explore biomarkers that may predict the pharmacologic activity of NC762

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.

2.2.2 Secondary Endpoints

1) Assessment of PK of NC762 include individual NC762 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

3) Tumor biopsy analyses to evaluate downregulation of B7-H4 expression and changes in tumor infiltrating lymphocytes after NC762 treatment.

2.2.3 Exploratory Endpoints

1) Immunogenicity, defined as the occurrence of ADA to NC762 will be determined.

2) Biomarker effects of NC762 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).
- The expression of additional histological biomarkers may also be assessed.

3 STUDY DESIGN

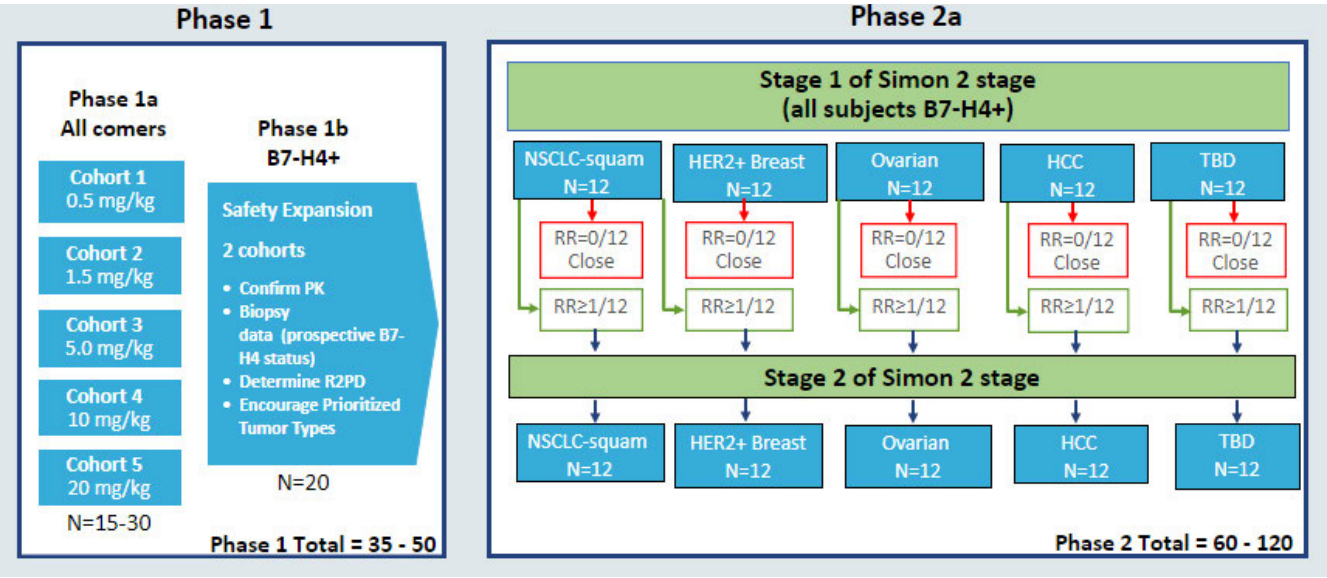
3.1 Description of the Study

This is an open-label, nonrandomized, Phase 1/Phase 2 study to determine the safety and tolerability, define the MTD or PAD, and to assess the preliminary efficacy of NC762 in subjects

with advanced or metastatic solid tumors. Subjects will receive NC762 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 non-small cell lung (squamous cell), hepatocellular carcinoma, HER2+ breast, and ovarian cancer, or other tumor type as identified with emerging data.

Figure 1: 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 NC762.

A minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (0.5 mg/kg; 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 NC762 at a lower dose, and/or investigate 0.5 mg/kg 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 NC762 will proceed according to Table 2.

Throughout the treatment period, if > 33% of subjects (a minimum of 6 subjects) experience a ≥ Grade 3 toxicity related to study drug after completing ≥ 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 ≥Grade 3 toxicity in previous treatment cycles. The cohorts and dose levels are shown in Table 2.

Table 2: NC762 Dose Levels and Cohorts

Cohort	Dose of NC762
1 (Starting dose)	0.5 mg/kg
2	1.0 mg/kg
3	5.0 mg/kg
4	10 mg/kg
5	20 mg/kg

3.1.1.2 Phase 1b – Safety Expansion

To evaluate additional PD activity of NC762 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. Doses of NC762 (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 20 evaluable subjects will be enrolled in the Phase 1b safety expansion, with each cohort enrolling up to 10 additional subjects; pre-screening and on treatment biopsies will be required. Sites will be encouraged to enroll prioritized tumor types. During Phase 1b Safety Expansion, subjects with CLIA validated B7-H4+ staining on the membrane of tumor cells confirmed by tumor biopsies at pre-screening will be considered eligible to enroll.

If < 3 of 10 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 NC762 in subjects with advanced or metastatic non-small cell lung (squamous cell), hepatocellular carcinoma , HER2+ breast, and ovarian cancer, or other tumor identified based upon emerging data. Each cohort will be comprised of an individual tumor type. Biopsies at pre-screening and on treatment will be required of all enrolled Phase 2 subjects. During Phase 2 Dose Expansion, subjects with CLIA validated B7-H4+ staining on the membrane of tumor cells confirmed by tumor biopsies will be considered eligible to enroll.

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, 12 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, 12 additional evaluable subjects will be enrolled in the cohort (Stage 2), for at least 24 evaluable subjects per cohort.

Subjects will continue to receive NC762 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 ≥ 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 ≥ Grade 3 toxicity related to study drug after completing ≥ 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 170 evaluable subjects may be enrolled in this study.

- Phase 1a Dose Escalation – Approximately 15–30 evaluable subjects
- Phase 1b Safety Expansion – Approximately 20 additional evaluable subjects
- Phase 2 Dose Expansion – Up to 120 evaluable subjects (up to 60 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-treatment samples) will 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 approximately 30 days.

Note: During Phase 1b and Phase 2, potential subjects will be consented first using short-form ICF prior to pre-screening biopsy to evaluate for B7-H4+. Confirmed B7-H4+ subjects must be consented a second time using the main ICF, prior to completing remainder of screening activities for study participation.

Subjects will continue to receive NC762 until disease progression or unacceptable toxicity, if the subject is deriving benefit and has not met any of the protocol-defined conditions for treatment withdrawal (see Section 5.5.1). Subjects who continue to receive benefit from NC762 after completing 12 months of treatment will have the option to enroll into a separate expanded access protocol; safety assessments will be continued. If the subject discontinues treatment with NC762, 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.

   Note: During Phase 1b and Phase 2, potential subjects will be consented first using short-form ICF prior to pre-screening biopsy to evaluate for B7-H4+. Confirmed B7-H4+ subjects must be consented a second time using the main ICF, prior to completing remainder of screening activities for study participation.

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), breast cancer, urothelial carcinoma, and other tumors considered likely to respond to immune checkpoint inhibitors.

   b. Phase 1b and Phase 2: Subjects with non-small cell lung cancer (squamous), hepatocellular carcinoma (HCC), HER2+ breast, ovarian cancer, with CLIA validated B7-H4+ staining confirmed by tumor biopsy. 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 (must allow for adequate sample of tissue from appropriate site).

   Note: For Phase 1a, 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 NC762-01 study procedure) before signing consent may be utilized to evaluate for B7-H4+ with the medical monitor's approval.

8) All females of child-bearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy and are not postmenopausal, defined as ≥ 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 < 1.5×10^9/L.
   b. Platelets < 100×10^9/L.
   c. Hemoglobin < 9 g/dL or < 5.6 mmol/L.
   d. Serum creatinine > 1.5 × 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) ≥ 2.5 × ULN with the following exceptions: Subjects with documented liver metastases AST and/or ALT ≤ 5 × ULN. Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 ×ULN.
   f. Total bilirubin ≥ 1.5 × ULN.
      Note: Subjects with documented Gilbert's syndrome with elevated total bilirubin may be permitted to enroll after consultation with the medical monitor.
   g. International normalized ratio (INR)/prothrombin time (PT) > 1.5 × ULN *or* Activated partial thromboplastin time (aPTT) > 1.5 × ULN, except for subjects receiving therapeutic anticoagulation.

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. ≤ 14 days for chemotherapy, targeted small molecule therapy, hormonal therapy or radiation therapy.
      Note: Subjects must not have had radiation pneumonitis because of a treatment.
      Note: A 1-week washout is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval.
      Note: Bisphosphonates and denosumab are permitted medications; continuation of hormonal therapy is allowed for CRPC patients.
   b. ≤ 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. ≤ 28 days for a prior mAb used for anticancer therapy except for denosumab.
   d. ≤ 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 physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.
   e. ≤ 28 days or 5 half-lives, $t_{½}$, (whichever is longer) before the first dose for all other investigational study drugs or devices. For investigational agents with long

half-lives (e.g., > 5 days), enrollment before the fifth $t_{½}$ requires medical monitor approval.

f. ≤ 14 days for a COVID-19 vaccine.
Note: For 2-dose COVID-19 vaccines, subjects must wait at least 14-days after 2nd dose of vaccine prior to receiving the first dose of the study drug.

5) Has not recovered to ≤ 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 (≤ 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 30 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) Documented known activating or driver mutations (i.e. EGFR mutations/amplification, BRAF mutations, ALK alterations, etc.) which have not been previously treated with a standard of care targeted therapy.

    Note: Documented microsatellite instability (MSI) status is not an exclusionary criterion.

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

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

14) Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV), unless the hepatitis 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.

15) Known history of HIV (HIV 1 or HIV 2 antibodies).

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

17) 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.

18) 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 subject number with the first 3 digits serving as the site number. The subject numbering process 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 NC762; 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 (NC762) 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). NC762 is formulated at a nominal concentration of 60 mg/mL in 20 mM Histidine, 8% (w/w) sucrose, 0.03% (w/w) Polysorbate 80 pH 5.5. The drug can be diluted as low as 0.04 mg/mL; additional information can be found in the NC762 IB. The infusion site should not be used for blood sampling.

5.2.2 Supply Packaging and Labeling

Study drug will be packaged as open-labelled supplies, each vial will be labelled 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 ≥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 3, 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 3: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
Any ≥ Grade 3 nonhematologic toxicity **EXCEPT** the following: • Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. • An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. • Asymptomatic changes in amylase and lipase. • Single or non-fasting elevations in blood glucose (i.e., blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions). **Note**: Any grade ≥3 non-hematologic toxicity should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.
Hematologic toxicity
• Grade 3 thrombocytopenia with clinically significant bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia. • ≥ Grade 3 febrile neutropenia (absolute neutrophil count < 1.0×10^9/L and fever > 38.3°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting study drug. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
Immune-related toxicity
• ≥ Grade 2 ocular irAEs • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy • Grade 4 irAEs regardless of duration.

General
• 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. • Combined elevations in serum ALT >3 times the upper limit of normal (ULN) **and** bilirubin >2 ULN in the absence of alkaline phosphatase (ALP) elevation (<2 ULN)   ○ 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. • Any death not clearly due to the underlying disease or extraneous causes.
MTD
• In Phase 1 of the study, the MTD will be defined as 1 dose level below that at which ≥ one-third of subjects in a cohort have DLTs. • In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of DLTs occurs in > 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.
MNTD
• Throughout the treatment period, if > 33% of subjects (minimum of 6 subjects) experience a ≥ Grade 3 toxicity related to study drug after completing ≥ 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.

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). **Note**: Patients who have >28-day treatment delay must discontinue from further treatment.

Instructions for dose modifications and interruptions are outlined in Table 4. 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 (≤ 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. The reason for interruption/delay should be documented in the subject's study record.

Table 4: Rules for Interruption and Restarting of Study Drug

NCI CTCAE v5.0 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.[a]	Toxicity does not resolve within 4 weeks (28 days) of last dose, except by approval of the medical monitor. *or* 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.
[a] No more than 2 dose reductions of study drug are permitted (see Table 2). 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

NC762 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 NC762, 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 5. Detailed supportive care guidelines for specific irAEs can be in 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 5: Supportive Care Guidelines for Subjects Exhibiting Immune-Related Adverse Events

NCI CTCAE v5.0 Grade/Severity	Supportive Care
Grade 1 (mild)	• Monitor symptoms and provide symptomatic treatment.
Grade 2 (moderate)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Consider systemic corticosteroids per institutional standard of care.
Grade 3-4 (severe–life-threatening)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Administer corticosteroids per institutional standard of care. • More potent immunosuppressive therapies should be considered for events not responding to systemic steroids after discussing with the medical monitor. • 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.

5.4.8 Management of Infusion Reactions

Table 6 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 6: Infusion Reaction Treatment Guidelines

NCI CTCAE v5.0 Grade/Severity	Treatment	Premedication at Subsequent Dose Administration
Grade 1: 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.
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be interrupted until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.	Subject may be premedicated 1.5 h (± 30 min) prior to infusion with the following: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).

NCI CTCAE v5.0 Grade/Severity	**Treatment**	**Premedication at Subsequent Dose Administration**
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). *or* Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine 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.	No subsequent dose.

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
- ≥ 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)

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.

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 follow-up visits. 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) ≤ 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, inhaled or topical steroids, systemic steroids at doses ≤ 10 mg/day prednisone or equivalents, and 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 the study drug **and** during the 28-day DLT period.

  Note: For 2-dose COVID-19 vaccines, subjects must wait at least 14-days after 2nd dose of vaccine prior to receiving the first dose of the study drug.
- 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 7: Schedule of Assessments (Ph. 1 & Ph. 2)

Visit Day	Protocol Section	Pre-Screening[c] *(Phase 1b and Phase 2 ONLY)*	Screening (Approx. 30 days prior to C1D1)	Treatment[a]					Post-Treatment[b]		
				All Cycles	Cycles 1 & 5[d]			Every 8/12 weeks[n]	EOT	Safety Follow-Up 1	Safety Follow-Up 2
				Day 1	Day 2	Day 3	Day 8	Disease Status			
Evaluation/Window (Range)		**≥ 7 Days prior to initiation of Screening**	**~Day - 30 to - 1**	**± 3 days (after Cycle 1)**			**± 1 day**	**± 7 days**		**30 days (+ 7 days)**	**90 days (+ 7 days)**
ADMINISTRATIVE PROCEDURES											
Pre-Screening Consent	7.1	X									
Main Informed consent	7.1		X								
I/E criteria	4	X	X								
Demographics	7.2	X	X								
Cancer History and Diagnosis	7.2.2	X	X								
Medical History[e]	7.2		X								
Prior/concomitant meds	7.3	X[f]									
Administer NC762	5.2.1			X							
Post-study anticancer therapy status	7.4								X	X	X
CLINICAL PROCEDURES/ASSESSMENTS											
Comprehensive PE[g]	7.5.2.1		X								
Targeted physical assessment[f]	7.5.2.2			X			X		X		
Vital signs and weight	7.5.3		X	X[h]			X		X		
ECOG performance	7.5.2.1		X	X			X		X		
12-lead ECG[i] (Table 12)	7.5.4		X[j]	X[k]					X[j]		
AE assessment	7.5.1	X[l]									
Laboratory assessments[m] (Table 8 and Table 9)	7.5.5		X	X			X		X		
PK/ADA and PD assessments[m] (Table 10 and Table 11)	7.7 and 7.8			X	X[n]	X[n]	X		X		
Tumor Biopsy[o]	7.8.1	X	X	X					X		
EFFICACY MEASUREMENTS											
Radiologic assessments	7.6.1.1		X[p]					X[q]	X[r]		

a Treatment cycles after Cycle 1 will begin every 14 days (± 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 the last dose of study drug if the EOT visit was not performed). Safety follow-up must be performed before any new systemic anticancer therapy is started regardless of whether it occurs before the end of the 30- or 90-day safety follow-up period. Safety follow-up may be performed by phone.
c **For Phase 1b and Phase 2 only**: Potential subjects will be consented using short-form ICF prior to pre-screening biopsy to confirm B7-H4+ tumor status. Initial review of eligibility criteria will begin and Demographics and Cancer History and Diagnosis must be documented at time of pre-screening. Collection of AEs and Concomitant medications directly related to study procedures will also begin at pre-screening. Subjects confirmed as B7-H4+ must be consented a second time, prior to completing the remainder of screening activities for study participation.
d 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.
e Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.
f 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.
g Comprehensive Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. The comprehensive physical examination 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).
h During Cycle 1 subjects will be required to stay at the study site for safety observation for 4 hours post end of infusion. At 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 (±10 minutes) thereafter. On Day 1 of all subsequent cycles, subjects will be required to be observed for a minimum of 1 hour post end of infusion or per PI discretion if indicated. After cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose and at end of infusion (+10 minutes). Subjects will also be assessed for the onset of acute AEs.
i 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.
j A single 12-lead ECG should be performed anytime at Screening and EOT.
k ECGs will be performed on Day 1 of Cycles 1 and 5, in conjunction with PK samples at the following timepoints: pre-infusion and post-infusion (+30 minutes). Additional ECGs should be performed per PI discretion if any clinically significant abnormal findings are noted or as indicated.
l AEs will be collected after ICF has been signed and through end of study. 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;
m If a central line is used for study drug infusion, collect blood samples via peripheral blood draw to prevent sample contamination.
n Visit/lab assessments on Day 2 and 3 are required for Phase 1 subjects only.
o For Phase 1a, tumor biopsies are optional. Biopsies are required for all Phase 1b and Phase 2 subjects. Biopsies will be collected at Pre-Screening (Phase 1b and Phase 2 only), Screening (Phase 1 subjects), 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.
p 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.
q On-study imaging will be performed at Week 8 (during Cycle 4), then every 8 weeks (56 days ± 7 days) for the first 6 months, and then every 12 weeks (84 days ± 7 days) thereafter. 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.
r 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 ± 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 ± 7 days) for the first 6 months (from first dose) and then every 12 weeks (84 days ± 7 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 8: Schedule of Local Laboratory Assessments (Ph. 1 & Ph. 2)

Visit Day	Protocol Section	Screening[a]	Treatment			Post-Treatment
			C1 and C5		Day 1 of All Other Cycles	EOT
			D1[a]	D8	D1[c]	
Evaluation/Window (Range)		**~Day - 30 to - 1**	**Pre-infusion[b,c]**	**± 1 day**	**- 3 days**	
Comprehensive serum chemistries[d]	7.5.5	X	X	X	X	X
Hematology with differential[e]	7.5.5	X	X	X	X	X
Coagulation panel[f]	7.5.5	X	X	X	X	X
Urinalysis[g]	7.5.5	X	X	X	X	X
Endocrine function tests[h]	7.5.5	X	X	X	X	X
Hepatitis B and C[i]	7.5.5.2	X				
Serum pregnancy test (childbearing females only)[j]	7.5.5.1	X[j]				X
Urine pregnancy test (childbearing females only)[k]	7.5.5.1		X[l]		X[l]	

a Serum chemistry, hematology, coagulation, urinalysis, and endocrine function tests must be performed during screening period and on Cycle 1 Day 1.
b Laboratory samples on Cycle 1 Day 1 must be collected 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 administration of study drug.
c After Cycle 1, pre-infusion 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 9.
e Hematology required analytes in Table 9.
f Coagulation panel required analytes in Table 9. 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 9. 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 9.
i Hepatitis testing required analytes in Table 9.
j Pregnancy testing is required for females of child-bearing potential. A serum pregnancy test must be performed at screening.
k If positive, confirm results with serum pregnancy test.
l For women of child-bearing potential only, Day 1 urine pregnancy must be performed and resulted before study drug administration.

Table 9: 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 **Absolute values must be provided for the following WBC differential laboratory results:** 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* ***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.	PT aPTT INR
		Endocrine Function Tests	**Pregnancy Testing**	
		Thyroid-stimulating hormone Free thyroxine (Free T4) Total triiodothyronine (Total T3) Free triiodothyronine (Free T3)	Female subjects of childbearing potential require a serum test at screening and EOT and thereafter, urine pregnancy tests will be done on Day 1 of all cycles. Pregnancy tests (serum or urine) should be repeated if required by local regulations.	

HDL = high-density lipoprotein; LDL = low-density lipoprotein; WBC = white blood cell.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

Table 10: Schedule of Pharmacokinetic and Anti-Drug Antibody Sampling

PK/ADA Subject Schedule				
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) • 4 h (± 30 min) post-infusion
Cycle 1 Day 2	X		PK	• 24 h (± 60 min) post-infusion
Cycle 1 Day 3	X		PK	• 48 h (± 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	• Pre-infusion
Cycle 5 Day 1	X	X	PK and ADA	• Pre-infusion
	X		PK	• Post-infusion (+ 10 min) • 4 h (± 30 min) post-infusion
Cycle 5 Day 2	X		PK	• 24 h (± 60 min) post-infusion
Cycle 5 Day 3	X		PK	• 48 h (± 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 11: 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[c]		• Anytime
	Day 1 of Cycles 3, 5, 7, 11, and 23	X	X	• Pre-infusion
Serum correlative sample for cytokine levels	Cycle 1 Day 1	X	X	• Pre-infusion • Post-infusion (+10 min)
	Cycle 1 Day 2	X[c]		• Anytime
	Cycle 5 Day 1	X	X	• Pre-infusion • Post-infusion (+10 min)
	Cycle 5 Day 2	X[c]		• Anytime
	Cycle 11 Day 1	X	X	• Pre-infusion • Post-infusion (+10 min)
Biopsies[a]	Pre-Screening/ Screening	X	X	• Anytime
	Cycle 3[b]			
	EOT			
Plasma ctDNA	Cycle 1 Day 1	X	X	• Pre-infusion

a Tumor biopsies are optional for Phase 1a. An optional Screening biopsy may be performed for subjects who consent in Phase 1a. Pre-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 1st on-treatment scan (~ Cycle 4) and subsequent dose.

c Sample collection is only applicable for Phase 1 subjects.

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).

Note: During Phase 1b and Phase 2, potential subjects will be consented first using short-form ICF prior to pre-screening biopsy to evaluate for B7-H4+. Confirmed B7-H4+ subjects must be consented a second time using the main ICF, prior to completing remainder of screening activities for study participation.

Screening assessments should be completed within a period of 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 occur within approximately 30 days after the subject has signed the main ICF.

Subjects will have regularly scheduled study visits on Day 1 of every cycle ± 3 days (after Cycle 1). Additional visits will be required on Day 2 and 3 (for subjects enrolled in Phase 1 only) and at Day 8 (all subjects) of Cycles 1 and 5. During study visits, the subject will have clinical and laboratory assessments as outlined in Table 7 and Table 8. 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 10 and Table 11). 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. At 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 (±10 minutes) thereafter. On Day 1 of all subsequent cycles subjects will be required to be observed for a minimum of 1 hour post end of infusion or per PI

discretion if indicated. After cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose and at end of infusion (+10 minutes).

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.

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 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 the end of the 30- or 90-day 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 ± 7 days) for the first 6 months and then every 12 weeks (84 days ± 7 days) thereafter, 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.

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, non-drug 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 Status

The investigator or qualified designee will review all new systemic anticancer therapy initiated after the last dose of study drug. 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, semi recumbent, or sitting position after 5 minutes of rest. At 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 (±10 minutes) thereafter. After cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose and at end of infusion (+10 minutes). 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 at least 15 minutes after a blood collection. All 12-lead ECGs should be acquired using an ECG system with analysis and printing capabilities. ECG assessments will be done as single assessments as per Table 12.

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

On Day 1 of Cycles 1 and 5, ECGs will be collected in conjunction with PK samples at the following timepoints: pre-infusion and post-infusion. Additional ECGs should be performed per PI discretion if any clinically significant abnormal findings are noted or as indicated.

The 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 12: Timing of Electrocardiograms

ECG Schedule[c]	Timing of Sample		
Study Visit	**Any Time**	**Pre-infusion**	**Post-infusion**
Screening	X		
C1D1		X[a]	X[b]
C5D1		X[a]	X[b]
EOT	X		

[a] ECGs should be conducted within 30 minutes prior to the PK blood draw.

[b] ECGs should be started 15 to 30 minutes after the PK sample is drawn.

[c] Additional ECGs should be performed per PI discretion if any clinically significant abnormal findings are noted or as indicated.

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 7 and Table 8. Table 9 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 screening period and on Cycle 1 Day 1.

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 for women of childbearing potential locally as outlined in Table 8, 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 8) to rule out hepatitis infection; required analytes are shown in Table 9. 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 13 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 13: 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

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 7). 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 (during Cycle 4) and then every 8 weeks (56 days ± 7 days) for 6 months and then every 12 weeks (84 days ± 7 days) thereafter until disease progression is determined. Imaging assessments may be done more frequently if clinically indicated. **Imaging should not be delayed for delays in cycle starts**. If imaging is delayed, the missed scan should be conducted as soon as possible, and all subsequent scans must remain on schedule (every 8 weeks relative to the first dose of NC762) 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 ± 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 ± 7 days) for the first 6 months

(from first dose) and then every 12 weeks (84 days ± 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 10. 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-infusion 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, plasma and serum samples will be collected at the visits outlined in Table 11. 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 tumor biopsies will be collected as specified below:

- **Pre-Screening (mandatory in Phase 1b and Phase 2):** A pre-screening biopsy will be obtained to identify potential non-small cell lung cancer (squamous), hepatocellular carcinoma (HCC), HER2+ breast, ovarian cancer subjects with confirmed B7-H4+ on the membrane of tumor cells. Biopsy will be submitted to a central lab for processing and analysis using a CLIA-validated assay to detect B7-H4+. Subjects confirmed as B7-H4+ will qualify to move forward with the remainder of screening activities to assess eligibility for study participation.

- **Screening (optional, Phase 1a):** An optional Screening biopsy may be performed for subjects who consent in Phase 1a.
- **On-treatment (mandatory in Phase 1b Safety Expansion and Phase 2):** A second mandatory on-treatment biopsy must be obtained anytime during Cycle 3 ± 1 week (prior 1st 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, Phase 1 and Phase 2):** 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.

Details and methods for obtaining, processing, and shipping the fresh tumor biopsy samples will be provided in the Biopsy Collection 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). Other assays relevant to the objectives of the study, such as flow cytometry analysis of intracellular cytokines, and circulating tumor DNA in plasma may be performed based upon emerging data.

7.8.3 Serum Pharmacodynamic Assessment

Serum samples will be evaluated to assess evidence of NC762 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: IFNγ, IL-2, IL-4, IL-6, and TNFα) pre- and on-treatment with NC762. 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 11. 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. 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. Conditions that were already present at the time of informed consent should be recorded on the Medical History 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 14 to estimate the grade of severity.

Table 14: NCI CTCAE v5.0 Grading Scale

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

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 to 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 NC762 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 NC762, 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:

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 NC762. 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 NC762. 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 170 eligible subjects in Phase 1 and Phase 2 (50 + 120) 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 NC762. A 3 + 3 study design will be used for dose escalation. A maximum of 5 dose levels will be tested. Therefore, a maximum of 30 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 NC762 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 20 subjects in the Phase 1b). If < 3 of 10 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 NC762. 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, 12 subjects will be enrolled; if no responses are observed, then the cohort will be discontinued. If at least 1 response is observed, then 12 additional subjects will be enrolled (Stage 2), for a maximum of 24 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 15) 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 15: 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	> 38ºC	< 35.5ºC
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 16). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 16: 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}, $t_{½}$, 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 ± 7 days) post-dosing for 6 months and then every 12 weeks (84 ± 7 days) thereafter. 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.

  PFS = (progressive disease, death, or censored date) – (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).

  OS = (Death or LKA date) – (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 NC762.

The immunogenic potential of NC762 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 NC762-01 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 Trial Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Trial 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 Trial 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 Trial 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 Trial 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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13 APPENDIX

Appendix 1: Signatures

Sponsor Signature(s)

A Phase 1/ Phase 2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC762 in Subjects with Advanced or Metastatic Solid Tumors

I agree to the terms of this protocol.

[redacted] _____

[redacted]

[redacted]

[redacted]
[redacted]

[redacted]

Sponsor Signature(s)

A Phase 1/ Phase 2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC762 in Subjects with Advanced or Metastatic Solid Tumors

I agree to the terms of this protocol.

[redacted] _____

[redacted]

[redacted]
[redacted]

[redacted]

Signature of Principal Investigator

A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC762 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) _____

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)

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

Grade	Eastern Cooperative Oncology Group (ECOG)
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light 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-Age) * Mass (in kg)] \ [72 * 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

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

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

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

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

Calculation for Obesity

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

Example:

Subject weight = 160. Subject ideal weight = 120

160-120 = 40

40 /120 = 0.33

0.33 x 100% = 33%

(Cockcroft and Gault 1976)