A PHASE 1B/2, OPEN-LABEL, SAFETY, TOLERABILITY AND EFFICACY STUDY OF NC410 PLUS PEMBROLIZUMAB FOR PARTICIPANTS WITH ADVANCED UNRESECTABLE AND/OR METASTATIC IMMUNE CHECKPOINT INHIBITOR (ICI) REFRACTORY SOLID TUMORS OR ICI NAÏVE MSS/MSI-LOW SOLID TUMORS

Sponsor Protocol Number: NC410-02

IND Number: 141990

Investigational Products: NC410
LAIR-2 IgG1 Fusion Protein
Pembrolizumab
Humanized Monoclonal Antibody Against PD-1 (IgG4)

Phase of Study: 1b/2

Sponsor:
NextCure, Inc.
9000 Virginia Manor Road, Suite 200
Beltsville, MD 20705 USA
Phone: 240-399-4900
Email: NCClin@nextcure.com

Medical Monitor:
Han Myint, MD
Chief Medical Officer
NextCure, Inc.
Phone: 240-399-4900
Email: NCClin@nextcure.com

Amendment 2.0 Version 3.0	23-APR-2024

PROTOCOL SYNOPSIS

HYPOTHESIS

A combination of Pembrolizumab and NC410 will result in clinical benefit for participants with advanced unresectable and/or metastatic Immune Checkpoint Inhibitor (ICI) refractory solid tumors OR ICI naïve MSS/MSI-low solid tumors.

STUDY OBJECTIVES AND ENDPOINTS

Phase 1b

Primary

Study Objectives	Study Endpoints
• To evaluate the safety and tolerability of NC410 in combination with Pembrolizumab in Phase 1b	• Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). **Note**: Toxicity grading per NCI CTCAE v5.0 • The recommended Phase 2 dose (RP2D) of NC410 when combined with standard dose Pembrolizumab will be defined in participants with advanced unresectable and/or metastatic ICI refractory solid tumors (regardless of MSI status) OR ICI naïve MSS/MSI-low solid tumors

Secondary

Study Objectives	Study Endpoints
• To evaluate the clinical benefit of NC410 in combination with Pembrolizumab	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on RECIST v1.1 as assessed by the investigator b. Overall Survival (OS)
• To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of NC410 when combined with Pembrolizumab	• Assessment of PK of NC410 concentration in serum, as well as assessment of combination treatment on the PK/PD profile

Exploratory

Study Objectives	Study Endpoints
• To assess the immunogenicity of NC410 when combined with Pembrolizumab	• Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC410 will be determined

• To evaluate efficacy in CRC participants with and without liver metastasis at baseline.	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab in CRC participants with and without liver metastasis , including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on RECIST v1.1 as assessed by the investigator. b. Overall Survival (OS)
• To evaluate efficacy using iRECIST for immune-based therapeutics	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on iRECIST as assessed by the investigator
• To explore biomarkers that may predict the pharmacologic activity of NC410 when combined with Pembrolizumab	• Biomarker effects of NC410 in combination with Pembrolizumab in peripheral blood and tumor tissue will be assessed, including but not limited to the following: a. Whole blood immune cell population profiling/immunophenotyping b. Serum markers of inflammation or immune modulation (cytokine & chemokine levels) c. Soluble LAIR-1, LAIR-2 and C1q levels d. Collagen derived products including, but not limited to, C4G, Pro-C3, Pro-C6, etc. e. Tumor biopsy analyses to evaluate the tumor microenvironment in tumor tissue and immune cell infiltrates at baseline and following treatment, and correlate expression levels with efficacy including, but not limited to, MSI or MSS status, PD-L1 expression, LAIR-1 and collagen staining. f. The expression of additional histological biomarkers may also be assessed based on emerging data
• To characterize the effect on markers of immunity of NC410 when combined with Pembrolizumab	• The effect on markers of immunity may be explored as determined based on emerging data of NC410 in combination with Pembrolizumab

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCR = Disease Control Rate; DoR = Duration of Response; ICI = Immune Checkpoint Inhibitor; LAIR = Leukocyte-Associated Immunoglobulin-like Receptor; MSI = microsatellite instable; MSS = microsatellite stable; NCI = National Cancer Institute; ORR = Objective Response Rate; OS = Overall Survival; PD = Pharmacodynamics; PD -L1 = Programmed Cell Death Protein Ligand 1; PFS = Progression -free Survival; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; R2PD = recommended Phase 2 dose.

Phase 2	
Primary	
Study Objectives	**Study Endpoints**
• To evaluate the anti-tumor activity of NC410 in combination with Pembrolizumab in Phase 2	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab including: a. Objective Response Rate (ORR) based on RECIST v1.1 as assessed by the investigator
Secondary	
• To evaluate the clinical benefit of NC410 in combination with Pembrolizumab in Phase 2	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Duration of Response (DoR), Disease Control Rate (DCR) and Progression-free Survival (PFS) based on RECIST v1.1 as assessed by the investigator b. Overall Survival (OS)
• To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profile of NC410 when combined with Pembrolizumab	• Assessment of PK of NC410 concentration in serum, as well as assessment of combination treatment on the PK/PD profile
• Continue to evaluate the safety and tolerability of NC410 in combination with Pembrolizumab	• Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). **Note**: Toxicity grading per NCI CTCAE v5.0
Exploratory	
• To assess the immunogenicity of NC410 when combined with Pembrolizumab	• Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC410 will be determined
• To evaluate efficacy using iRECIST for immune-based therapeutics	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on iRECIST as assessed by the investigator

• To explore biomarkers that may predict the pharmacologic activity of NC410 when combined with Pembrolizumab	• Biomarker effects of NC410 in combination with Pembrolizumab in peripheral blood and tumor tissue will be assessed, including but not limited to the following: a. Whole blood immune cell population profiling/immunophenotyping b. Serum markers of inflammation or immune modulation (cytokine & chemokine levels) c. Soluble LAIR-1, LAIR-2 and C1q levels d. Collagen derived products including, but not limited to, C4G, Pro-C3, Pro-C6, etc. e. Tumor biopsy analyses to evaluate the tumor microenvironment in tumor tissue and immune cell infiltrates at baseline and following treatment, and correlate expression levels with efficacy including, but not limited to, MSI or MSS status, PD-L1 expression LAIR-1 and collagen staining. f. The expression of additional histological biomarkers may also be assessed based on emerging data
• To characterize the effect on markers of immunity of NC410 when combined with Pembrolizumab	• The effect on markers of immunity may be explored as determined based on emerging data of NC410 in combination with Pembrolizumab

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCR = Disease Control Rate; DoR = Duration of Response; LAIR = Leukocyte-Associated Immunoglobulin-like Receptor;; NCI = National Cancer Institute; ORR = Objective Response Rate; OS = Overall Survival; PD = Pharmacodynamics; PD -L1 = Programmed Cell Death Protein Ligand 1; PFS = Progression -free Survival; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors.

STUDY DESIGN

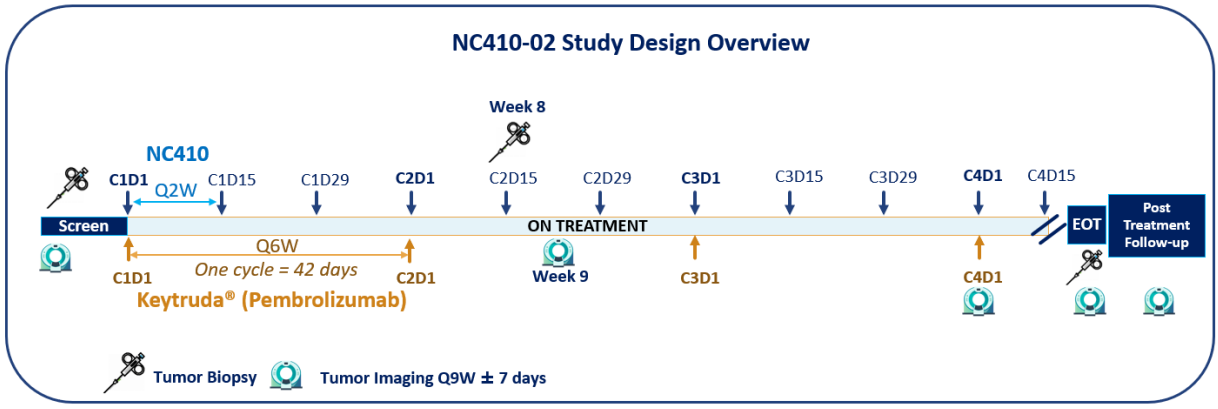
Description and Duration

This is an open-label, non-randomized, Phase 1b/2 study to determine the safety and tolerability of NC410 when combined with a standard dose of Pembrolizumab. This study will also assess the clinical benefit of combination therapy in participants with advanced unresectable and/or metastatic ICI refractory solid tumors OR ICI naïve MSS/MSI-low solid tumors. Participants will receive Pembrolizumab on Day 1 of each 42-day cycle followed by administration of NC410. Additional doses of NC410 will be given on Day 15 and Day 29 of each 42-day cycle as shown in Figure S1.

The study will be conducted in 2 parts:

- **Phase 1b** – Dose Escalation of NC410 to determine the optimal dose administration schedule and RP2D when combined with a standard dose of Pembrolizumab.
- **Phase 2** – Dose Expansion to evaluate the recommended Phase 2 dose (RP2D) of NC410 in combination with a standard dose of Pembrolizumab.

Figure S1: Study Design Overview



Abbreviations: C = cycle; D = Day; EOT = end of treatment; Q2W = every 2 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks.

Participants will continue until progressive disease, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant receives 18 treatments (approximately 2 years) of Pembrolizumab, or administrative reasons requiring cessation of treatment. **Note**: In the event NC410 is discontinued due to toxicity, continued treatment with pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Participants who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until progressive disease, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed for overall survival (OS) until death, withdrawal of consent, or the end of the study. After the end of treatment, each participant will be followed for 30 days for AE monitoring. Serious adverse events (SAE) and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier.

Study Phase and Cohorts

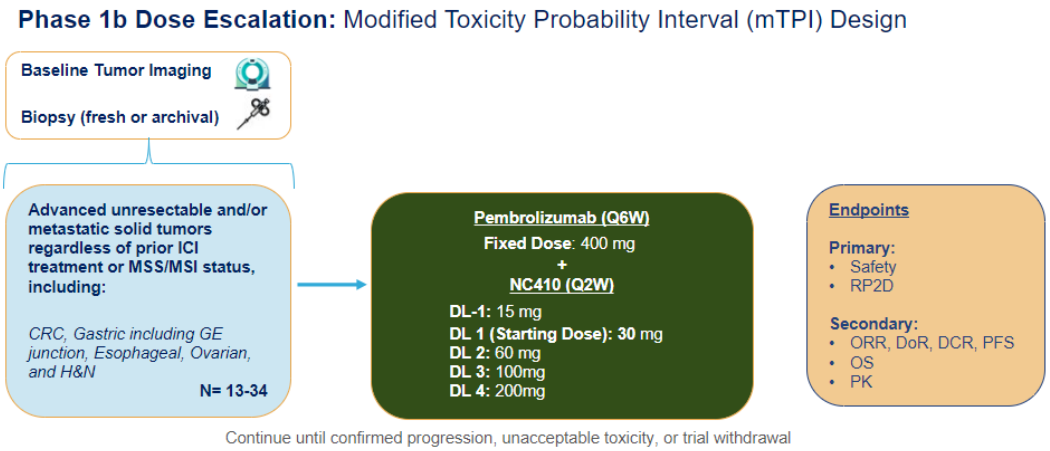
Phase 1b– Dose Escalation of NC410 + Pembrolizumab

The Phase 1b portion of the study will enroll participants with advanced unresectable and/or metastatic solid tumors including CRC (without liver metastasis), Gastric including GE junction, Esophageal, Ovarian, and H&N cancers regardless of prior treatment with ICIs or MSS/MSI status (Figure S2). At the sponsors discretion, the expansion of dose level cohorts may be limited to subjects with specific cancer types.

A modified Toxicity Probability Interval (mTPI) (Ji, 2013) with a target dose limiting toxicity (DLT) rate of approximately 30% will be applied for dose escalation and confirmation to determine a recommended Phase 2 dose (RP2D) for NC410 in combination with Pembrolizumab. There will be three dose levels of NC410 evaluated during the Phase 1b portion of the study. The pre-determined dose levels of NC410 (in combination with a fixed dose of Pembrolizumab of 400mg) will be explored independently. The dose levels are as follows:

- **Dose Level -1 (de-escalating dose):** 15 mg
- **Dose Level 1 (starting dose):** 30 mg
- **Dose Level 2:** 60 mg
- **Dose Level 3:** 100mg
- **Dose Level 4:** 200mg

Figure S2: Phase 1b Study Design



Abbreviations: CRC = colorectal cancer; DCR = Disease Control Rate; DoR = Duration of Response; GE = gastroesophageal; H&N = head and neck; MSI = microsatellite instable; MSS = microsatellite stable; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; PK = pharmacokinetics; Q2W = every 2 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 Dose.

The detailed rationale of starting dose selection and escalating dose levels is included under the "Rationale for Dose Selection" section of this synopsis.

The starting dose will be 30mg (Dose Level 1) of NC410. A de-escalation dose of NC410 is available if the starting dose of NC410 is deemed not tolerable in combination with Pembrolizumab. All dose escalation and de-escalation decisions will be based on the occurrence of DLTs at a given dose during the first 42-day period (i.e., Cycle 1) also referred to as the DLT observation period and will be made

jointly by the investigators and the sponsor. The dose of Pembrolizumab will remain constant at 400 mg Q6W for each dose level for NC410 and in each cohort through Phase 2.

In Figure S3 the number of participants treated is indicated in the columns and the number of participants who experienced a DLT is indicated in the rows. Dosing decisions include: escalate to the next higher dose (E), stay at the current dose (S), de-escalate to the next lower dose (D), and de-escalate to a lower dose and never test this dose again (i.e., unacceptably toxic dose; DU). Alternative dose levels or administration schedules may be considered pending safety review and emerging data.

Beginning with the starting dose level of NC410 (in combination with a fixed dose of Pembrolizumab), a minimum of 3 evaluable participants will be enrolled. A participant is considered evaluable if they have received 1) at least 1 dose of Pembrolizumab, 2) at least 1 dose of NC410, and 3) completed the 42-day DLT observation period. During dose escalation, a minimum of 3 participants are required at each dose prior to any dose escalation decisions being determined. Depending on accrual rate and occurrence of DLTs, additional participants (up to 10) may be enrolled at each dose cohort until the last of those participants completes the 42-day DLT observation period (i.e., Cycle 1).

For example, the dose escalation rules will proceed as follows if 3 participants are enrolled: if 0 out of the first 3 participants at a given dose level develops a DLT, then the dose can be escalated with the next available participant enrolled to the next level cohort without further expansion. If 1 out of the first 3 participants at a given dose level develops a DLT, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This dose would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (i.e., 4 out of 6 participants). If 2 out of the first 3 participants at a given dose level develop a DLT, the dose will be de-escalated to the lower dose level cohort. If 3 out of the first 3 participants at a given dose level develop a DLT, this dose will be considered unacceptably toxic (i.e., the dose will be de-escalated and never re-escalated to that dose again). The same principle will be applied whether 3, 4, 5 or 6 participants are enrolled in the same dose cohort according to Figure S3.

Based on the mTPI design, the number of participants who are enrolled at a dose, but are not yet fully evaluable for DLT assessment, may not exceed the number of remaining participants who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Figure S3. To determine how many more participants can be enrolled at a dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. In total, 3 to 14 participants may be enrolled at a given dose level during dose escalation.

During or after the completion of Dose Escalation, based on the totality of available data, one or more dose levels may be backfilled/expanded for additional safety, PK, and pharmacodynamic analyses for the purpose of dose optimization. All participants in backfill/dose expansion will be evaluated for DLTs, and the doses will be monitored for emerging safety issues.

Dose escalation and confirmation will end after at least 10 evaluable participants have been treated at any of the selected doses. The pool-adjacent-violators-algorithm (Ji, 2013) will be used to estimate the DLT rates across doses.

The dose with an estimated DLT rate closest to 30% may be treated as a preliminary maximum tolerated dose (MTD). The totality of the data will be considered before a dose is selected to carry forward to Phase 2 and the escalation schedule may be adjusted based on PK, PD, and safety data emerging throughout the study to determine the RP2D. Note that while 30% was the target toxicity rate used to generate the guidelines in Figure S3, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%. If a participant is not evaluable for the DLT observation period for any reason, they may be replaced with the next available participant if escalation or de-escalation rules have not been fulfilled.

The dose level cohort which is determined to be the RP2D will be expanded until at least 10 participants have been dosed and observed for the duration of the 42-day DLT Observation period before moving onto Phase 2 Dose Expansion.

Figure S3: Dose-Finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose											
Number of participants with at least 1 DLT	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

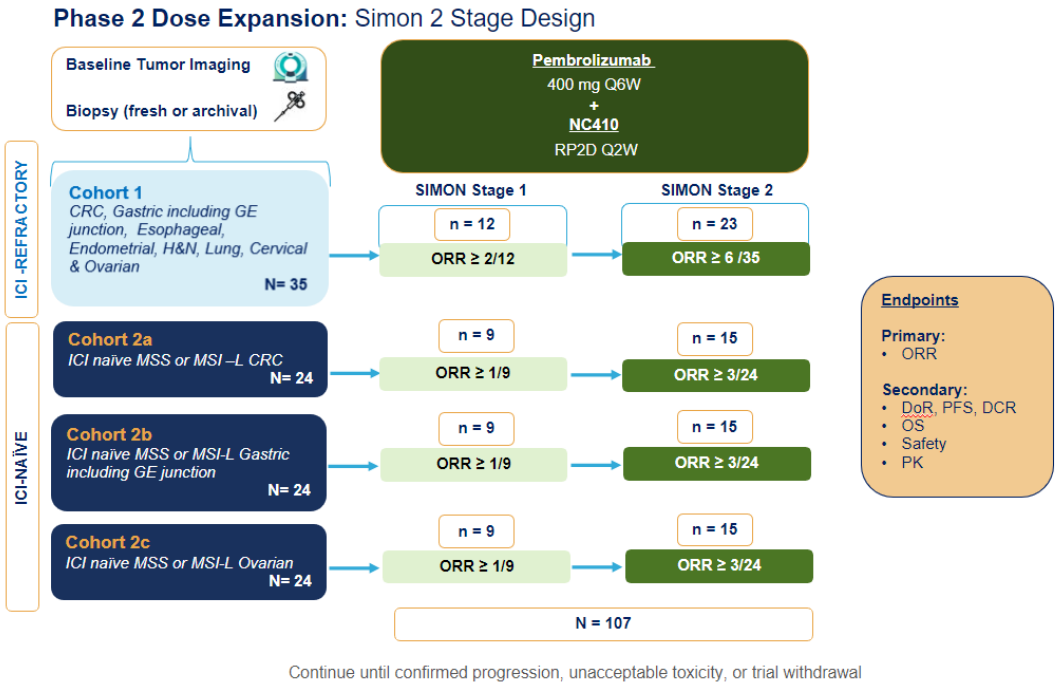
E = Escalate to the next higher dose; S = Stay at the current dose; D = De-escalate to the next lower dose; DU = The current dose is unacceptably toxic.
Target toxicity rate = 30%
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03

Abbreviation: DLT = Dose-Limiting Toxicity.

Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the clinical benefit of the RP2D of NC410 in combination with standard dose Pembrolizumab in participants with advanced unresectable and/or metastatic solid tumors across different cohorts as outlined below based on previous ICI refractory or naïve history (Figure S4).

Figure S4: Phase 2 Study Design



Abbreviations: CRC = colorectal cancer; DCR = Disease Control Rate; DoR = Duration of Response; GE = gastroesophageal; H&N = head and neck; ICI = Immune Checkpoint Inhibitor; ORR = Objective Response Rate per RECIST v1.1; OS = Overall Survival; PFS = Progression-Free Survival; PK = pharmacokinetics; Q2W = every 2 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 Dose.

The study will enroll ICI Refractory solid tumors in Cohort 1 and ICI Naïve solid tumors in Cohorts 2a, 2b, and 2c as described below. MSS or MSI-L status must be confirmed prior to entry into these cohorts (either by historical result or during screening).

- **Cohort 1:** ICI Refractory Solid Tumors (CRC MSI-H, Gastric including GE junction, Esophageal, Endometrial H&N, Lung, Cervical and Ovarian cancer).
- **Cohort 2a:** ICI Naïve MSS or MSI-L CRC
- **Cohort 2b:** ICI Naïve MSS or MSI-L Gastric including GE junction
- **Cohort 2c:** ICI Naïve MSS or MSI-L Ovarian

For the ICI-Naïve group, each cancer type will be considered its own cohort. **Note**: For Cohorts 2a, 2b, and 2c, the cancer types were selected based on their anticipated MSS/MSI-L status (approximately 90-95%) across these tumor types. MSS or MSI-L status must be confirmed prior to entry into cohorts 2a, 2b, and 2c (either by historical result or during screening). MSI-H CRC or Gastric including GE junction who have been treated with ICI and become refractory to ICI will be enrolled into Cohort 1 (ICI refractory Solid Tumors).

An optimal 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. For Cohort 1, 12 evaluable participants will be enrolled in the cohort in Stage 1; if 1 or fewer responses are observed within the cohort then the cohort will be discontinued. If at least 2 responses are observed, 23 additional evaluable participants will be enrolled in the cohort (Stage 2), for at least 35 total evaluable participants in the cohort. For Cohorts 2a, 2b, and 2c, 9 evaluable participants will be enrolled in each of the cohorts in Stage 1; if no response is observed within the cohort then the cohort will be discontinued. If at least 1 response is observed, 15 additional evaluable participants will be enrolled in the cohort (Stage 2), for at least 24 total evaluable participants per cohort.

STUDY RATIONALE

Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma.(Dudley, 2005; Hunder, 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Okazaki, 2001; Greenwald, 2005).

The structure of murine PD-1 has been resolved (Zhang, 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand

binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki, 2001; Chemnitz, 2004; Sheppard, 2004; Riley, 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry, 2005; Francisco, 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target in the tumor microenvironment (TME) and an effective approach for cancer therapy.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, Pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (Pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

Several other checkpoint inhibitors have gained substantial attention in cancer treatment during the last decade due to the durability of the responses and increased survival benefit. Some favorable factors emerge as predictors of response to ICI: presence and activation status of tumor infiltrating T cells, expression of PD-L1 or high tumor mutational burden (TMB). Presence of multiple neoantigens originating from highly mutated tumors led to increase in tumor infiltrating T cells favoring ICI responses. Similarly, Mis-matched Repair Deficient (dMMR) tumors have 10 to 100 folds increase in somatic mutations compared to pMMR (Mis-matched Repair Proficient) tumors. This hypothesis led to Lee and Le in 2015 to have shown that dMMR CRC and dMMR non-CRC tumors had excellent response to Pembrolizumab when there was no response to Pembrolizumab in pMMR CRC (Le, 2015). Subsequently, the FDA has approved Pembrolizumab in unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. This favorable response to ICI is hypothesized to be due to abundance of neoantigens with accompanying immune cell infiltration in the TME. In contrast, response to ICI in patients with MSS/MSI-L/pMMR tumors with low mutational load and absence of "immune-competent" TME, is disappointing. Therefore, there is high unmet medical need to explore new strategies to enhance responses to ICI in MSS/MSI-L tumors.

Furthermore, only 30% of patients with advanced cancers of certain types could benefit from ICI monotherapy or in combination with chemotherapy or other agents and the majority lost responses due to a variety of resistant mechanisms: emergence of T-regs; Myeloid derived suppressor cells (MDSC); M2 macrophages; TGF- β driven collagens that promote anti-PD-1/PD-L1 resistance and through LAIR-1-mediated immunosuppression including preventing CD8+ and CD4+ T cell proliferation and activation. Beyond these factors, the presence of a collagen-dense extracellular matrix (ECM) is increasingly being recognized as a critical determinant of tumor responses to ICI therapy. Collagens can be secreted in the TME by cancer-associated fibroblasts (CAFs), cancer cells, and macrophages. Functioning as a physical barrier to immune cell infiltration into the tumor, a collagen-dense ECM has been shown to suppress antitumor immunity and to associate with PD-1/PD-L1 resistant tumors (Peng, 2020).

Abnormalities in the ECM of the TME support tumor progression, lead to immune dysfunction, and provide targets for cancer therapeutics. LAIR-1 is an inhibitory receptor expressed on the cell surface of

several immune cell subsets. LAIR-1 binding to collagens inhibits immune cell function. LAIR-2 is a soluble homolog of LAIR-1 that binds to and out competes LAIR-1 binding to collagens and serves as a natural decoy to promote immune function. LAIR-2 is capable of blocking LAIR-1 functional interactions with ligands, resulting in improved immune function on multiple immune cell subsets.

It has been shown that certain tumors that have higher collagen deposition result in either inherent or acquired resistance to PD-1/PD-L1 blockade due to alternative immune suppression pathways and decreased total intra-tumoral CD8+ T cells (Peng, 2020). This phenomenon of collagen-induced CD8+ T cell immune suppression is due to over expression of LAIR-1 on immune cells, and enhanced collagen production in part driven by increased TGF-β signaling upon treatment with PD-1/PD-L1 blockade. Given LAIR-2 binds with higher affinity to collagen than LAIR-1, overexpression of LAIR-2 results in blockade of LAIR-1 signaling, sensitizing resistant tumors to PD-1 blockade and markedly reducing tumor growth and metastasis.

NC410 is a dimeric form of the LAIR-2 protein fused to a human Fc domain of the immunoglobulin (Ig) subtype IgG1. NC410 targets tumor collagen to reverse LAIR-1-mediated immunosuppression, as well as induce ECM remodeling to promote immune cell infiltration and function in the TME. NC410-01 is a Phase 1/2 study to determine the safety, tolerability, DLT, MTD, RP2D, and to assess preliminary efficacy, and explore predictive and pharmacodynamic biomarkers in participants with advanced or metastatic solid tumors with measurable disease (NCT04408599). Inhibition of the PD-1 pathway in the TME with Pembrolizumab in conjunction with NC410 should promote immune cell activation coupled with ECM remodeling, and further T cell infiltration into the TME, providing a novel and improved treatment approach for participants with ICI refractory advanced metastatic solid tumors regardless of MSI status or MSS or MSI-low advanced unresectable and/or metastatic solid tumors.

Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Strome, 2003; Blank, 2004; Hirano, 2005; Curran, 2010; Pilon-Thomas, 2010; Weber, 2010; Spranger, 2014). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome, 2003; Nomi, 2007; Zhang, 2009; Curran, 2010; Pilon-Thomas, 2010). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran, 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Pembrolizumab IB).

Pre-clinical studies in mouse models (HT-29, P815) with NC410 have been shown to enhance T cell expansion (both CD4+ and CD8+ cells), increase production of IFN-g and granzyme B, and anti-tumor effect in dose-dependent fashion. Because tumor-associated collagen induces CD8+ T cell exhaustion through LAIR-1-SHP-1 signaling, overexpression of LAIR-2 to inhibit LAIR-1 binding to collagen, resulted in reduction of tumor growth in a lung tumor model. Moreover, when LAIR-2 overexpression was combined with anti-PD-1 treatment growth and metastasis were significantly reduced within 1 week of treatment and was sustained throughout the course of treatment (Peng, 2020). Furthermore, NC410 with anti-PD-1 inhibitor has been shown consistently to reduce tumor burden.

RATIONALE FOR DOSE SELECTION

Pembrolizumab Dosing

The planned dose of Pembrolizumab for this study is 400 mg every 6 weeks (Q6W), in combination with NC410 given on Days 1, 15 and 29 during each 42-day cycle.

A 400 mg Q6W dosing regimen of Pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W Pembrolizumab is currently appropriate

(Lala, 2020). Specifically, the dosing regimen of 400 mg Q6W for Pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- Pharmacokinetic (PK) simulations demonstrating that in terms of Pembrolizumab exposures
  - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
  - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of Pembrolizumab.
  - Exposure-response (E-R) for Pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.

NC410 Dosing

NC410 was studied in advanced metastatic solid tumors in a Phase 1/2 monotherapy trial, NC410-01, which explored various dose levels from 3mg Q2W (Cohort 1) to 200mg Q2W (Cohort 7). Based on pre-clinical studies of NC410 it was expected that a pharmacologically active dose will emerge between Cohort 5 (60 mg Q2W) to Cohort 7 (200 mg Q2W). Preliminary safety, tolerability, and PK/PD data obtained from NC410-01 participants up to Cohort 7 at 200 mg Q2W appears to suggest NC410 is safe and well-tolerated with early evidence of disease control and evidence of immune modulation: time -dependent increases in CD4+ and CD8+ T cells without concomitant increase in LAIR-1 expression, and early evidence of ECM remodeling- trends in increase in C4G and decrease in PRO-C3 and PRO-C6.

Given the data obtained from the NC410 monotherapy trial, the following dose levels of NC410 administered Q2W in combination with a standard dose of Pembrolizumab (400 mg Q6W) will be evaluated in this Phase 1b:

- **Dose Level -1:**15 mg
- **Dose Level 1 (starting dose):** 30 mg
- **Dose Level 2:** 60 mg
- **Dose Level 3:** 100mg
- **Dose Level 4:** 200mg

The starting dose of Dose Level 1 (30mg Q2W) was chosen based on safety and efficacy data available from the monotherapy study. Furthermore, pre-clinical data of NC410 from mouse models shows 10 mg/kg (equivalent to 60 mg in an 80 kg human) as the pharmacologically active dose. Alternative dose levels or administration schedules may be considered pending safety review and emerging data from the Phase 1 monotherapy study and this Phase 1b combo study.

TARGET PARTICIPANT POPULATION

Men and women, 18 years or older participants with advanced unresectable and/or metastatic ICI refractory solid tumors or ICI naïve MSS/MSI-low solid tumors. Participants must provide written informed consent and have adequate organ function. Participants must present with measurable disease based on RECIST v1.1 and consent to have a non-target lesion biopsied prior to and during treatment. Note: Archival tissue may be submitted in place of fresh biopsy at pre-treatment. On-treatment biopsy will be fresh biopsy. If a participant is scheduled to have a tumor biopsy for the purposes of this study

and it is subsequently determined that tumor tissue cannot safely be obtained, then the participant may still enroll or continue treatment in the study. Participants with certain serious medical conditions (in addition to the diagnosis of cancer) would be excluded from participation in the trial.

ELIGIBILITY CRITERIA

Inclusion Criteria:

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

1) The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
2) Be ≥ 18 years of age on day of signing informed consent.
3) Participant with histologically or cytologically confirmed diagnosis of the following advanced unresectable and/or metastatic solid tumors:

a. **Phase 1b**: Participants with solid tumors, that are known to be associated as MSS/MSI-low in the majority including: CRC (without liver metastasis), Gastric including GE junction, Esophageal, Ovarian, and H&N cancer (regardless of prior treatment with ICIs). **Note**: Participants must have had disease progression after at least one line of systemic standard of care therapy prior to enrollment. Participants who discontinue standard treatment due to intolerance or refuse standard treatment will also be eligible to enroll.

b. **Phase 2 ICI Refractory Solid Tumors (Cohort 1):**

c. Participants with solid tumors including CRC, Gastric including GE junction, Esophageal, Endometrial, H&N, Lung, Cervical and Ovarian cancer.

d. Participants must have progressed on treatment with an anti-PD1/L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

   i. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

4) Has demonstrated disease progression after PD-1/L1 as defined by RECIST v1.1.

a. **Phase 2 ICI naïve Solid Tumors (Cohorts 2a-2c):**

   i. Tumors known to be associated with MSS/MSI-low status such as CRC, Gastric including GE junction, and Ovarian cancer where participants have not been previously treated with ICIs.

   Note: Participants must have had disease progression after at least one line of systemic standard of care therapy prior to enrollment. Participants who discontinue standard treatment due to intolerance or refuse standard treatment will also be eligible to enroll.

   Note: Confirmation of MSS/MSI status should be assessed prior to study entry (either by historical result or during screening).

5) A male participant must agree to use contraception and refrain from sperm donation or expecting to father a child, from Screening through the treatment period and for at least 120 days after the last dose of study treatment.
6) A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

a. Not a woman of childbearing potential (WOCBP)

b. A WOCBP who agrees to follow contraceptive guidance outlined in Section 6.2 from Screening through the treatment period and for at least 120 days after the last dose of study treatment.

7) Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

8) Able to provide tumor tissue sample at Screening, archival (≤ 5 years old) or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. If a tumor block is unavailable, a minimum of 8 unstained slides may be submitted.

Note: If a participant is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the participant may still enroll in the study.

9) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

10) Life expectancy greater than or equal to 12 weeks as judged by the Investigator.

11) Have adequate organ function as defined in the following table (Table S1). Specimens below must be collected within 10 days prior to the start of study treatment (i.e. C1D1).

Table S1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal.

[1] Criteria must be met without packed red blood cell (PRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

[2] Creatinine clearance (CrCl) should be calculated per institutional standard.

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

Note: Participants with liver metastases at baseline may be inviting DLTs and labs should be reviewed and discussed with the medical monitor prior to initial dosing.

Exclusion Criteria:

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

Medical Conditions

Pregnancy Exclusion

1) A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

2) Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137), and was discontinued from that treatment due to a Grade 3 or higher irAE.
3) Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (could consider shorter interval for kinase inhibitors or other short half-life drugs) prior to treatment.

Note: Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤ 2 requiring treatment or hormone replacement may be eligible.

Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.

4) Has received prior radiotherapy within 2 weeks of start of study treatment or has had a history of radiation pneumonitis.

Note: Participants must have recovered from all radiation-related toxicities and do not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

5) Has received G-CSF or GM-CSF within 7 days prior to start of study treatment.
6) Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention.

Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

7) Receipt of COVID-19 vaccine within ≤ 14 days prior to first administration of study treatments.

Note: For 2-dose COVID-19 vaccines or COVID-19 booster, participants must wait at least 14-days after administration prior to beginning study treatment.

Prior/Concurrent Clinical Study Experience

8) Receipt of an investigational agent or use of an investigational device within 4 weeks prior to the first dose of study treatment.
9) Has had an allogeneic tissue/stem cell/solid organ transplant.

Diagnostic assessments

10) Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
11) Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of bladder, that have undergone potentially curative therapy are not excluded.

12) Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
13) Has severe hypersensitivity (≥ Grade 3), known allergy or reaction to Pembrolizumab, NC410, and/or any of their excipients.
14) Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
15) Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
16) Has an active infection requiring systemic therapy.
17) Has known active or history of HIV infection. No HIV testing is required unless mandated by local health authority.
18) Has known active Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

19) Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
20) Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

STUDY TREATMENTS

Pembrolizumab 400mg will be administered by intravenous (iv) infusion, over a minimum of 30 minutes on Day 1 of each 42-day cycle followed by NC410 iv infusion over a minimum of 30 minutes, with 30-60 minutes between administration of each study treatment (See NC410 Pharmacy Manual for additional details on 100mg and 200mg NC410 dosing) NC410 will also be administered on Day 1, Day 15 and Day 29 of each 42-day Cycle. Participants will continue until progressive disease, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant receives 18 treatments (approximately 2 years) of Pembrolizumab, or administrative reasons requiring cessation of treatment.

EVENTS OF CLINICAL INTEREST (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor within 24 hours of awareness by the Investigator.

Events of clinical interest for this trial include:

1) An overdose of Pembrolizumab or NC410 as defined in Section 9.1.3.1 – Reporting of an Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2) An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*.

   ***Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Medical Monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.
3) An adverse event meeting definition of a DLT as defined in Section 5.9

DOSE LIMITING TOXICITY

The evaluation period for DLTs will begin on Cycle 1 Day 1 and will continue up to 42 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 Section 5.9, except for events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.

Table S2: Definition of Dose-Limiting Toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

Nonhematologic toxicity

Any Grade 3 or Grade 4 non-hematologic laboratory value if:

- Clinically significant medical intervention is required to treat the participant or
- The abnormality leads to hospitalization, or
- The abnormality persists for >1 week.
- The abnormality results in a Drug-induced Liver Injury (DILI)

Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

- Any nonhematologic AE ≥ Grade 3 in severity should be considered a DLT, with the following exceptions:
  - Grade 3 fatigue lasting ≤ 3 days
  - Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheal per standard of care
  - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.

Hematologic toxicity

- Grade 4 hematologic toxicity lasting ≥7 days, except for thrombocytopenia:
  - Grade 4 thrombocytopenia of any duration.
  - Grade 3 thrombocytopenia with clinically significant bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent medical intervention).
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated

General

- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
- Missing >25% of NC410 doses as a result of drug-related AE(s) during the first cycle.
- Grade 5 toxicity.
- Any death not clearly due to the underlying disease or extraneous causes.

STATISTICAL ANALYSIS PLAN

The sample size for this study will be determined so that sufficient participants are included to assess the safety, tolerability, PK, and PD of repeat doses of NC410 in combination with a standard dose of Pembrolizumab.

Phase 1b

A modified Toxicity Probability Interval (mTPI) with a target dose limiting toxicity (DLT) rate of approximately 30% will be applied for dose escalation and confirmation to determine a recommended Phase 2 dose (RP2D) for NC410 in combination with Pembrolizumab. The sample size is not fixed and will vary based on emerging safety data at the doses studied for the Phase 1b.

Phase 2

For participants with ICI refractory solid tumors (regardless of MSI status), published data with ICI monotherapy suggests response rates of approximately 5-10% have been obtained. Thus, the objective for ICI- refractory cohort participants will be to improve upon this estimated 5-10% response rate. The trial will be conducted in the ICI refractory solid tumor cohort (CRC, Gastric including GE junction, Esophageal, H&N, Lung, Cervical and Ovarian cancers) using an optimal Simon two-stage Phase 2 trial design to rule out an unacceptably low response rate (CR+PR) of 10% (p0=0.10) in favor of an improved response rate of 30% (p1=0.30) in order to determine if there is a greater response to the combination of NC410 and Pembrolizumab in these participants. The null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. In the first stage, 12 evaluable participants will be accrued. If there are 1 or fewer responses in these 12 participants, enrollment in this arm will be stopped. If 2 or more of the first 12 participants have a response, then accrual would continue until a total of 35 evaluable participants have been treated in that arm. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. The null hypothesis will be rejected, further investigation of the drug is warranted, if 6 or more responses are observed in 35 participants. This design yields a type I error rate of .0977 and power of .9014 when the true response rate is 0.3.

For participants with ICI naïve and MSS or MSI low solid tumors (CRC, Gastric including GE junction, Ovarian), published data suggests response rates of approximately 0-10% with ICI have been obtained. Thus, the objective for this ICI- naïve participant will be to improve upon this estimated 0-10% response rate. The trial will be conducted in each disease cohort (CRC, Gastric including GE junction, and Ovarian) using an optimal Simon two-stage phase 2 trial design to rule out an unacceptably low response rate (CR+PR) of 5% (p0=0.05) in favor of an improved response rate of 25% (p1=0.25) in order to determine if there is a greater response to the combination of NC410 and Pembrolizumab in these participants. The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. In the first stage, 9 evaluable participants will be accrued. If there are 0 responses in these 9 participants, enrollment in corresponding arm will be stopped. If 1 or more of the first 9 participants have a response, then accrual would continue until a total of 24 evaluable participants have been treated each disease cohort in that arm. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. The null hypothesis will be rejected, further investigation of the drug is warranted, if 3 or more responses are observed in 24 participants. This design yields a type I error rate of .0931 and power of .9028 when the true response rate is 0.25.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bpm	Beats per Minute
BSA	Body Surface Area
C_{max}	Maximum Concentration of Drug
CNS	Central Nervous System
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte–Associated Protein 4
DC	Dendritic cell
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
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

Abbreviation or Specialized Term	Definition
Fc	Fragment crystallizable
FIH	First-in-Human
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
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
HPV	Human Papillomavirus
hr	Hours
IB	Investigator's Brochure
IBW	Ideal Body Weight
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICI	Immune Checkpoint Inhibitor
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
INR	International Normalized Ratio
INs	Investigator Notifications
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
iv	Intravenous
LAIR	Leukocyte-Associated Immunoglobulin-like Receptor
LKA	Last Known Alive
LPS	Lipopolysaccharide
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialized Term	Definition
min	Minutes
MNTD	Maximum Number of Tolerated Doses
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MSS	Microsatellite Stable
MSI-H	Microsatellite Instability- high
MSI-L	Microsatellite Instability-low
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Disease
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
ORR	Objective Response Rate
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

Abbreviation or Specialized Term	Definition
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
USA	United States of America

1. INTRODUCTION

This is an open-label, non-randomized, Phase 1b/2 study to determine the safety and tolerability of NC410 when combined with a standard dose of Pembrolizumab. The study will be conducted in 2 parts (Phase 1b and Phase 2). Phase 1b will utilize a modified Toxicity Probability Interval (mTPI) with a target dose limiting toxicity (DLT) rate of approximately 30% to determine the recommended Phase 2 dose (RP2D) of NC410 in combination with pembrolizumab. Phase 1b will enroll participants with advanced unresectable and/or metastatic solid tumors including CRC (without liver metastasis), Gastric including GE junction, Esophageal, Ovarian, and H&N cancers regardless of prior treatment with Immune Checkpoint Inhibitors (ICIs) or MSS/MSI status. At the sponsors discretion, the expansion of dose level cohorts in Phase 1b may be limited to subjects with specific cancer types. Phase 2 of the study will further evaluate the clinical benefit of the RP2D of NC410 in combination with standard dose Pembrolizumab in participants with advanced unresectable and/or metastatic solid tumors across different cohorts based on previous ICI-refractory or ICI-naïve history.

1.1. Background

1.1.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley, 2005; Hunder, 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) (Okazaki, 2001; Greenwald, 2005).

The structure of murine PD-1 has been resolved (Zhang, 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki, 2001; Chemnitz, 2004; Sheppard, 2004; Riley, 2009). The mechanism by which PD-1

down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry, 2005; Francisco, 2010). As a consequence, the PD 1/PD-L1 pathway is an attractive target in the tumor microenvironment (TME) is an effective approach for cancer therapy.

Several other checkpoint inhibitors have gained substantial attention in cancer treatment during the last decade due to the durability of the responses and increased survival benefit. Some favorable factors emerge as predictors of response to ICI: presence and activation status of tumor infiltrating T cells, expression of PD-L1 or high tumor mutational burden (TMB). Presence of multiple neoantigens originating from highly mutated tumors led to increase in tumor infiltrating T cells in favoring ICI responses. Similarly, Mis-matched Repair Deficient (dMMR) tumors have 10 to 100 folds increase in somatic mutations compared to pMMR (Mis-matched Repair Proficient) tumors. This hypothesis led to DT Le in 2015 to have shown that dMMR CRC and dMMR non-CRC tumors had excellent response to Pembrolizumab when there was no response to Pembrolizumab in pMMR CRC (DT Le 2015). Subsequently, the FDA has approved Pembrolizumab in unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. This favorable response to ICI is hypothesized to be due to abundance of neoantigens with accompanying immune cell infiltration in the TME. In contrast, response to ICI in patients with MSS/MSI-L/ pMMR tumors with low mutational load and absence of "immune-competent" TME, is disappointing. Therefore, there is high unmet medical need to explore new strategies to enhance responses to ICI in MSS/MSI-L tumors.

Furthermore, only 30% of patients with advanced cancers of certain types could benefit from ICI monotherapy or in combination with chemotherapy or other agents and the majority lost responses due to a variety of resistant mechanisms: emergence of T-regs; Myeloid derived suppressor cells (MDSC); M2 macrophages; TGF-β driven collagens that promote anti-PD-1/PD-L1 resistance and through LAIR-1-mediated immunosuppression including preventing CD8+ and CD4+ T cell proliferation and activation. Beyond these factors, the presence of a collagen-dense extracellular matrix (ECM) is increasingly being recognized as a critical determinant of tumor responses to ICI therapy. Collagens can be secreted in the TME by cancer-associated fibroblasts (CAFs), cancer cells, and macrophages. Functioning as a physical barrier to immune cell infiltration into the tumor, a collagen-dense ECM has been shown to suppress antitumor immunity and to associate with PD-1/PD-L1 resistant tumors (Peng, 2020).

It has been shown that certain tumors that have higher collagen deposition result in either inherent or acquired resistance to PD-1/PD-L1 blockade due to alternative immune suppression pathways and decreased total intra-tumoral CD8+ T cells (Peng, 2020). This phenomenon of collagen-induced CD8+ T cell immune suppression is due to over expression of LAIR-1 on immune cells, and enhanced collagen production in part driven by increased TGF-β signaling upon treatment with PD-1/PD-L1 blockade. Given LAIR-2 binds with higher affinity to collagen than LAIR-1, overexpression of LAIR-2 results in blockade of LAIR-1 signaling, sensitizing resistant tumors to PD-1 blockade and markedly reducing tumor growth and metastasis.

NC410 is a dimeric form of the LAIR-2 protein fused to a human Fc domain of the immunoglobulin (Ig) subtype IgG1. NC410 targets tumor collagen to reverse LAIR-1-mediated immunosuppression, as well as induce ECM remodeling to promote immune cell infiltration and function in the TME. NC410-01 is a Phase 1/2 study to determine the safety, tolerability, DLT, MTD, RP2D, and to assess preliminary efficacy, and explore predictive and pharmacodynamic

biomarkers in participants with advanced or metastatic solid tumors with measurable disease (NCT04408599). As a consequence, inhibition of the PD-1 pathway in the TME with Pembrolizumab in conjunction with NC410 should promote immune cell activation coupled with ECM remodeling, and further T cell infiltration into the TME, providing a novel and improved treatment approach for participants with ICI refractory advanced metastatic solid tumors regardless of MSI status or MSS or MSI-low advanced unresectable and/or metastatic solid tumors.

1.1.2. Overview of LAIR Biology

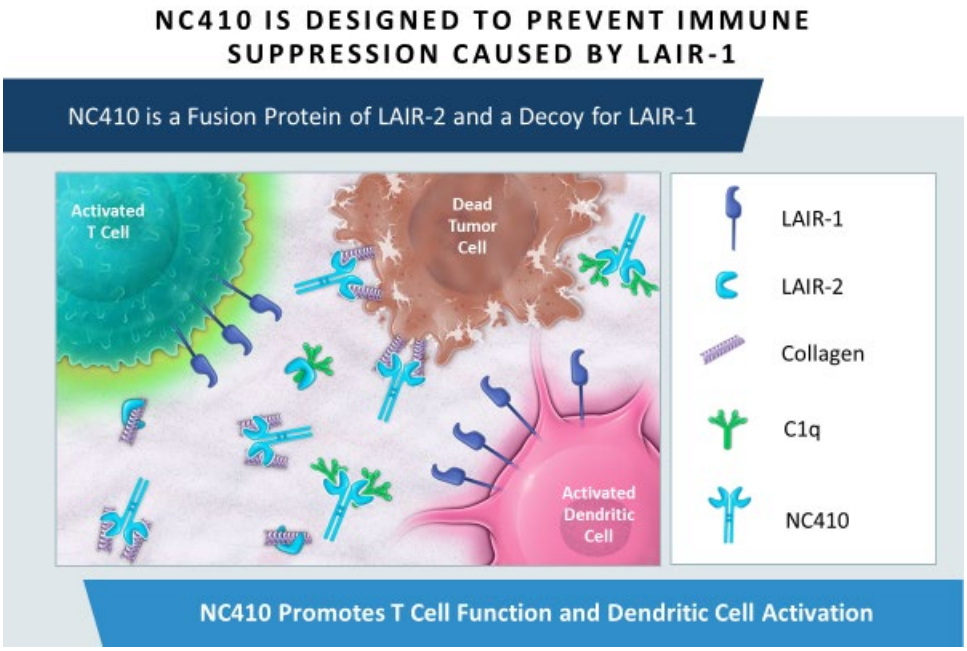
Abnormalities in the ECM of the TME support tumor progression, lead to immune dysfunction, and provide targets for cancer therapeutics. Leukocyte-Associated Immunoglobulin-like Receptor (LAIR)-1 and LAIR-2 are members of the Leukocyte Receptor Complex (LRC) on human chromosome 19 (Lebbink, 2008; Lebbink, 2009; Olde Nordkamp, 2011; Olde Nordkamp, 2014). LAIR-1 is a well-described co-inhibitory receptor expressed on several subsets of immune cells, and functions to delimit immune responses (Afshar-Kharghan, 2017; Pearce, 2018). LAIR-2 is a secreted protein with homology to the transmembrane protein LAIR-1 (Lebbink, 2008).

Studies have demonstrated that components of the ECM serve as ligands for a collagen-binding inhibitory receptor LAIR-1. LAIR-1 ligands include several types of collagens, as well as ligands with collagen domains including complement component C1q, Mannan Binding Lectin (MBL) and Surfactant Protein D (SP-D) (Lebbink, 2008; Lebbink, 2009; Olde Nordkamp, 2011; Olde Nordkamp, 2014). Furthermore, it is hypothesized that LAIR-1 expression on several subsets of leukocytes prevents optimal immune responses by limiting both innate and adaptive immune functionality. Overall, these data suggest that targeting the LAIR-1 pathway in cancer patients may be a rational approach to potentiate anti-tumor immunity.

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

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

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



Abbreviation: LAIR = Leukocyte-Associated Immunoglobulin-like Receptor.
NC410 binds to tumor-associated ligands (collagen and C1q) to block LAIR-1 inhibition and promote adaptive (T cells) and innate (dendritic cells) immune responses, as well as to activate macrophages, ultimately resulting in tumor cell killing.
Source: Data on file.

1.1.3. Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Strome, 2003; Blank, 2004; Hirano, 2005; Curran, 2010; Pilon-Thomas, 2010; Weber, 2010; Spranger, 2014). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome, 2003; Nomi, 2007; Zhang, 2009; Curran, 2010; Pilon-Thomas, 2010). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran, 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

Pre-clinical studies in mouse models (HT-29, P815) with NC410 have been shown to enhance T cell expansion (both CD4+ and CD8+ cells), increase production of IFN-g and granzyme B, and anti-tumor effect in dose-dependent fashion. Because tumor-associated collagen induces CD8+ T cell exhaustion through LAIR-1-SHP-1 signaling, overexpression of LAIR-2 to inhibit LAIR-1 binding to collagen, resulted in reduction of tumor growth in a lung tumor model. Moreover, when LAIR-2 overexpression was combined with anti-PD-1 treatment growth and metastasis were

significantly reduced within 1 week of treatment and was sustained throughout the course of treatment (Peng, 2020). Furthermore, NC410 with anti-PD-1 inhibitor has been shown consistently to reduce tumor burden.

1.1.4. Summary of Clinical Experience for NC410

Please refer to the NC410 IB for information on clinical trial experience with NC410.

1.2. Overview of Study Treatments

1.2.1. Overview of Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

1.2.2. Overview of NC410

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

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

- NC410 binds to LAIR-1 ligands including collagen, C1q, MBL and SP-D with high avidity and block the interaction of LAIR-1 to its ligands.
- NC410 reverses the inhibitory effects of collagen on the Lipopolysaccharide (LPS)-induced NF-κB and Interferon signaling, important signaling pathways leading to immune cell activation.
- NC410 promotes primary monocyte activation and differentiation toward a stimulatory macrophage phenotype.
- NC410 enhances human T cell expansion and activation in a dose-dependent manner, which correlates with anti-tumor efficacy mouse P815 and human HT29 tumor models and chemokines such as CXCL10, CXCL11 and CXCL12 productions.

- NC410 promotes T cell dependent cytokine and chemokine production in the tumor microenvironment that correlates with tumor control and promotes tumor remodeling as evidenced by changes in levels of collagen degradative products.

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

Refer to the Investigator's Brochure (IB) for detailed background information on NC410.

1.3. Rationale for Dose Selection

1.3.1. Pembrolizumab Dosing

The planned dose of Pembrolizumab for this study is 400 mg every 6 weeks (Q6W).

A 400 mg Q6W dosing regimen of Pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W Pembrolizumab is currently appropriate (Lala, 2020). Specifically, the dosing regimen of 400 mg Q6W for Pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- Pharmacokinetic PK simulations demonstrating that in terms of Pembrolizumab exposures
- Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
- Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of Pembrolizumab.
- Exposure-response (E-R) for Pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.

1.3.2. NC410 Dosing

NC410 was studied in advanced metastatic solid tumors in a Phase 1/2 monotherapy trial, NC410-01, which explored various dose levels from 3 mg Q2W (Cohort 1) to 200mg Q2W (Cohort7). Based on pre-clinical studies of NC410 it is expected that a pharmacologically active dose will emerge between Cohort 5 (60 mg Q2W) to Cohort 7 (200 mg Q2W). Safety, tolerability, and PK/PD data obtained from NC410-01 participants up to Cohort 7 at 200 mg Q2W suggest NC410 is safe and well-tolerated with an early evidence of disease control, evidence of immune modulation: time-dependent increases in CD4+ and CD8+ T cells without concomitant increase in

LAIR-1 expression, and early evidence of ECM remodeling- trends in increase in C4G and decrease in PRO-C3 and PRO-C6.

Given the data obtained from the NC410 monotherapy trial, the following dose levels of NC410 given Q2W in combination with a standard dose of Pembrolizumab (400 mg Q6W) will be evaluated in this Phase 1b:

- **Dose Level -1:** 15 mg
- **Dose Level 1 (starting dose):** 30 mg
- **Dose Level 2:** 60 mg
- **Dose Level 3:** 100mg
- **Dose Level 4:** 200mg

The starting dose of Dose Level 1 (30mg Q2W) was chosen based on safety and efficacy data available from the monotherapy study. Furthermore, pre-clinical data of NC410 from mouse models shows 10 mg/kg (equivalent to 60 mg in an 80 kg human) as the pharmacologically active dose. Alternative dose levels or administration schedules may be considered pending safety review and emerging data from the Phase 1 monotherapy study and this Phase 1b combo study

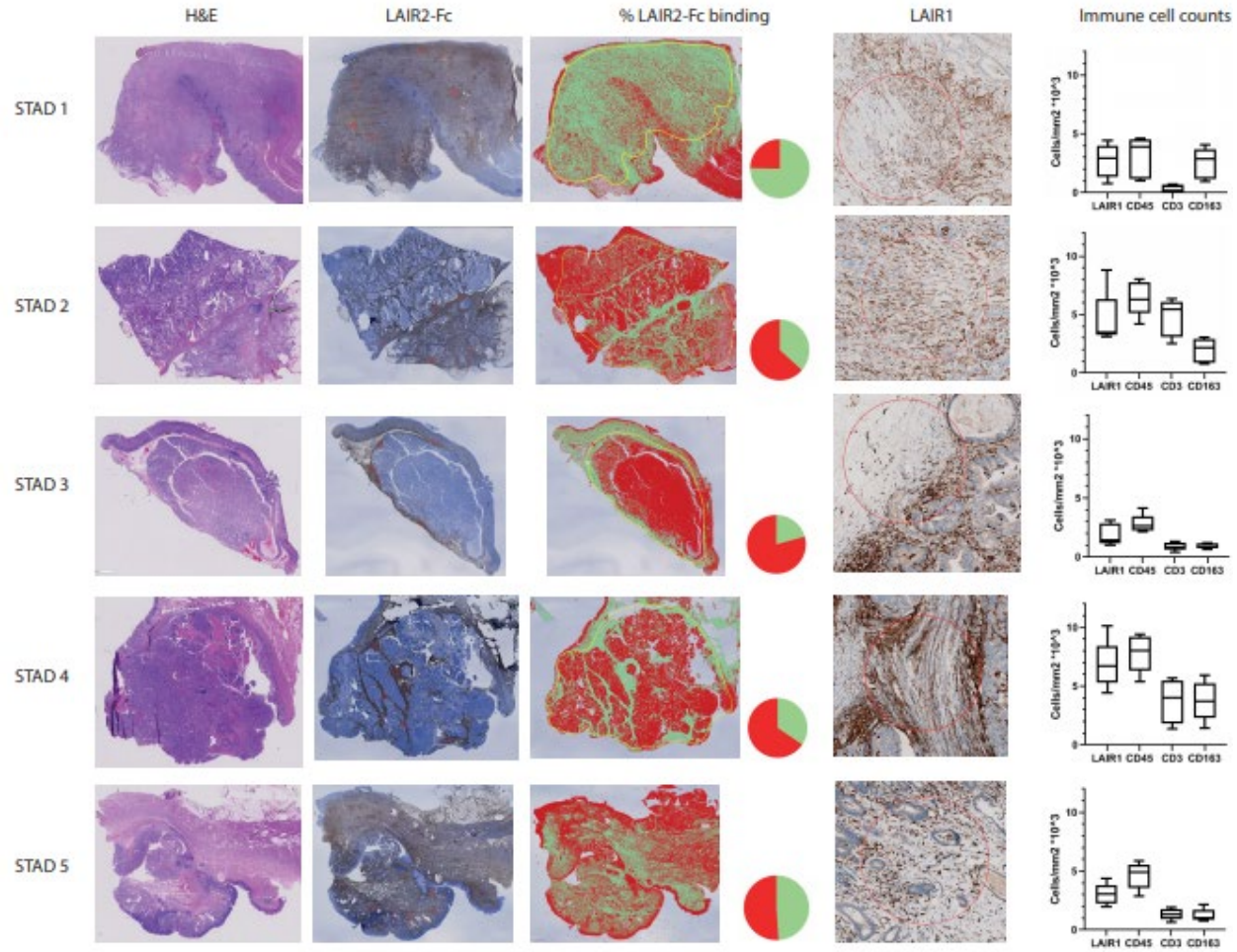
1.3.3. Rationale for Participant Population for Phase 2

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

- LAIR-1 expression in the TME
- CD163 M2-like macrophage marker, as assessed for relative increase in cancer vs normal tissues
- Analysis of several LAIR ligands, as assessed for overexpression in the TME in comparison to normal tissues

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

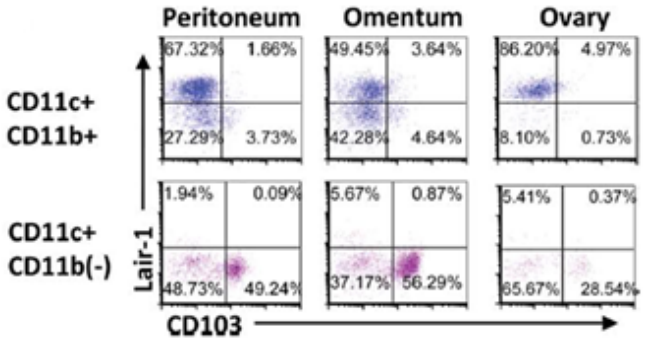
Figure 2: Immunohistochemistry Staining of Stomach Adenocarcinoma



Abbreviations: Fc = fragment crystallizable; H&E = hematoxylin and eosin; LAIR = Leukocyte Associated Immunoglobulin Like Receptor; STAD = stomach adenocarcinoma.
The analysis of five representative samples of stomach adenocarcinoma (STAD) is shown above. STAD tissues were analyzed by H&E staining, for LAIR-2-Fc (NC410) binding and by immuno staining of LAIR-1, CD45, CD3 and CD163 positive cells. For LAIR-2-Fc binding, brown staining indicates the binding of LAIR2-Fc, and blue staining is hematoxylin counterstaining indicating no binding by LAIR2-Fc. LAIR-2 Fc positive (green) and negative areas (red) were quantified as demonstrated in the associated pie charts. Five regions of interest (ROI) with a diameter of 600 µm were randomly chosen in the LAIR-2 Fc positive area for immune cell quantification. One of the ROIs was magnified to show the LAIR-1 staining. The graph shows the quantification of immune cells. The cell counts of LAIR-1$^+$, CD45$^+$, CD3$^+$ and CD163$^+$ cells within the five ROI were quantified and calculated as $\times 10^3/mm^2$.
Source: Ramos, 2021 and data on file.

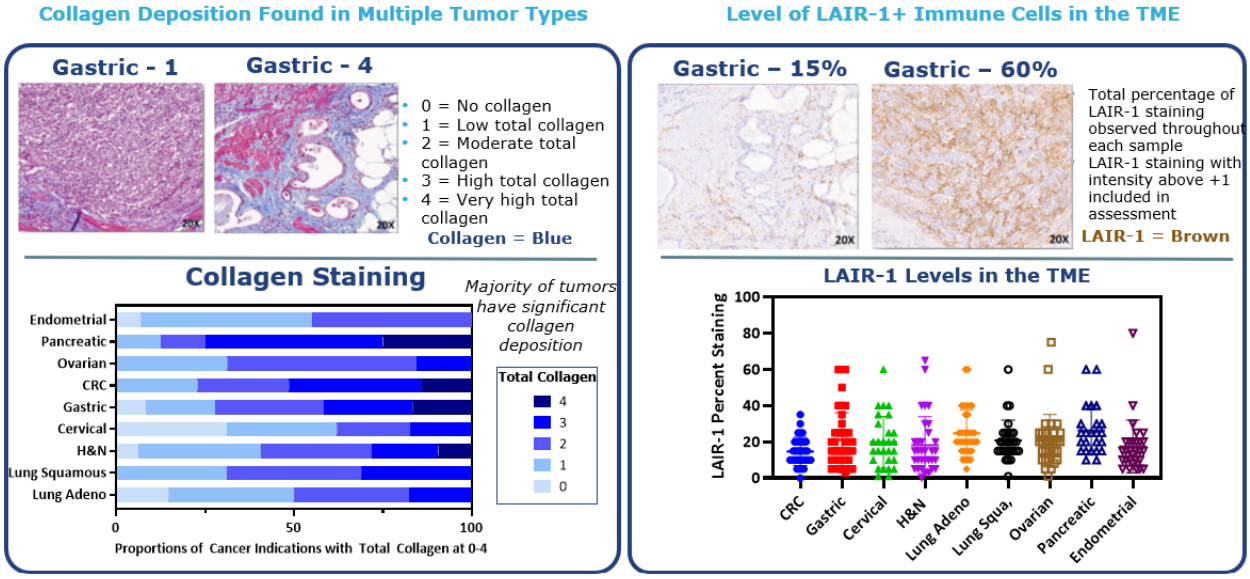
In addition to these described parameters, it is also known that LAIR-1 is highly restricted to the hematopoietic compartment and is only expressed on immune cells. Specifically, it has been observed that LAIR-1 expression is associated with suppressive immune cell populations in some cancers. A suppressive, but not stimulatory dendritic cell (DC) subpopulation, as well as suppressive macrophages express LAIR-1 in both mouse and human ovarian cancers (Figure 3), indicating that blockade of LAIR-1 in ovarian cancer should reverse immune suppression (Flies, 2016).

Figure 3: LAIR-1 is Expressed on Suppressive DCs in a Spontaneous Model of Ovarian Cancer



In the MISIIR Tg spontaneous model of ovarian cancer, LAIR-1 is expressed on CD11c+CD11b+ suppressive DCs at primary and metastatic sites of disease. LAIR-1 is not expressed on CD103+stimulatory DCs.
From: Flies, 2016.

Figure 4: Collagen Staining by Trichome Staining (Left) and LAIR-1 Staining in Immune Cells (Right) by IHC in Multiple Tumor Types



Abbreviations: Adeno = adenocarcinoma; CRC = colorectal cancer; H&N = head and neck; LAIR = Leukocyte Associated Immunoglobulin Like Receptor; TME = tumor microenvironment.

Source: Data on file.

To further elucidate the effects of NC410 in combination with pembrolizumab, a variety of different tumor types have been selected that have been shown to have collagen rich TME with LAIR-1 expressing immune cells such as HNSCC, CRC, gastric including GE junction, esophageal, endometrial and ovarian cancers (Figure 4). Furthermore, the majority of the aforementioned tumors are known to be associated with MSS/MSI-low status. Based on ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, it has been shown that MSI-H prevalence is very uncommon in CRC (17%), Endometrial (20%), Gastro-esophageal (13%), Ovarian (3.5-10%), and H&N (<1%). (Luchini, Annals of Oncology 2019).

Therefore, we anticipate the inverse to be true for the MSI-L, MSS, and pMMR status of these same tumors.

1.3.4. Rationale for Efficacy Endpoints

In Phase 1b, efficacy endpoints 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. In addition, overall survival will also be assessed.

In Phase 2, objective response rate (ORR) will be the primary endpoint, while duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival will be evaluated as secondary endpoints.

RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen with immunotherapy (Chiou, 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.

Treatment Beyond Progression

A minority of participants treated with immunotherapy drugs may derive clinical benefit despite initial evidence of progressive disease per RECIST v1.1. Immunotherapy treatment-induced enhanced inflammation within the tumor could lead to increase in tumor size. Also, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With additional treatment the anti-tumor activity may dominate the inherent tumor growth kinetics and become clinically apparent. Hence, it is important to avoid premature discontinuation of the study drug. The decision to continue treatment beyond Investigator-assessed RECIST should be discussed with Sponsor Medical Monitor and documented in study records. Participants should meet the following criteria to be considered for treatment beyond progression by RECISTv1.1:

- Participant is having clinical benefit as assessed by Investigator
- There is no rapid disease progression
- The study drug is well tolerated
- Participant has stable performance status
- Treatment beyond progression will not delay an immediate intervention to prevent serious complications of disease progression, for example, in CNS metastases

Participants undergoing treatment beyond progression will continue radiographic assessments in accordance with the Schedule of Activities. If there is an additional 10% increase in tumor burden with a minimum of 5 mm increase from time of initial progression, study drug treatment will be permanently discontinued unless the clinical judgement of the investigator is that continuing treatment is in the participant's best interest.

iRECIST

If radiologic imaging by the site identifies progressive disease by RECIST 1.1, and participant fulfills criteria for treatment beyond progression, participant management and tumor assessment may shift to iRECIST. Imaging should be repeated at least **4 weeks but no greater than 8 weeks later** in order to confirm progressive disease with the option of continuing treatment per below while awaiting radiologic confirmation of progression.

If repeat imaging shows < 20% increase in tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial progressive disease), and stable/improved nontarget disease (if identified as cause for initial progressive disease), progressive disease is not confirmed. Treatment may continue and subsequently follow a regular imaging schedule.

If repeat imaging confirms progressive disease due to any of the scenarios listed below, participants will be discontinued from study therapy (exception noted in Section 5.10.1).

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where progressive disease is confirmed at repeat imaging:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial progressive disease is worse (qualitative)
- New lesion resulting in initial progressive disease is worse (qualitative)
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

Participants that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease and should be discontinued from study treatment.

1.4. Research Hypotheses

A combination of Pembrolizumab and NC410 will result in clinical benefit for participants with advanced unresectable and/or metastatic Immune Checkpoint Inhibitor (ICI) refractory solid tumors OR ICI naïve MSS/MSI-low solid tumors.

2. STUDY OBJECTIVES AND ENDPOINTS

Phase 1b	
Primary	
Study Objectives	**Study Endpoints**
• To evaluate the safety and tolerability of NC410 in combination with Pembrolizumab in Phase 1b	• Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). **Note**: Toxicity grading per NCI CTCAE v5.0 • The recommended Phase 2 dose (RP2D) of NC410 when combined with standard dose Pembrolizumab will be defined in participants with advanced unresectable and/or metastatic ICI refractory solid tumors (regardless of MSI status) OR ICI naïve MSS/MSI-low solid tumors
Secondary	
Study Objectives	**Study Endpoints**
• To evaluate the clinical benefit of NC410 in combination with Pembrolizumab	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on RECIST v1.1 as assessed by the investigator b. Overall Survival (OS)
• To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of NC410 when combined with Pembrolizumab	• Assessment of PK of NC410 concentration in serum, as well as assessment of combination treatment on the PK/PD profile
Exploratory	
Study Objectives	**Study Endpoints**
• To assess the immunogenicity of NC410 when combined with Pembrolizumab	• Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC410 will be determined
• To evaluate efficacy in CRC participants with and without liver metastasis at baseline.	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab in CRC participants with and without liver metastasis , including: c. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on RECIST v1.1 as assessed by the investigator d. Overall Survival (OS)

• To evaluate efficacy using iRECIST for immune-based therapeutics	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on iRECIST as assessed by the investigator
• To explore biomarkers that may predict the pharmacologic activity of NC410 when combined with Pembrolizumab	• Biomarker effects of NC410 in combination with Pembrolizumab in peripheral blood and tumor tissue will be assessed, including but not limited to the following: a. Whole blood immune cell population profiling/immunophenotyping b. Serum markers of inflammation or immune modulation (cytokine & chemokine levels) c. Soluble LAIR-1, LAIR-2 and C1q levels d. Collagen derived products including, but not limited to, C4G, Pro-C3, Pro-C6, etc. e. Tumor biopsy analyses to evaluate the tumor microenvironment in tumor tissue and immune cell infiltrates at baseline and following treatment, and correlate expression levels with efficacy including, but not limited to, MSI or MSS status, PD-L1 expression, LAIR-1 and collagen staining. f. The expression of additional histological biomarkers may also be assessed based on emerging data
• To characterize the effect on markers of immunity of NC410 when combined with Pembrolizumab	• The effect on markers of immunity may be explored as determined based on emerging data of NC410 in combination with Pembrolizumab

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCR = Disease Control Rate; DoR = Duration of Response; ICI = Immune Checkpoint Inhibitor; LAIR = Leukocyte-Associated Immunoglobulin-like Receptor; MSI = microsatellite instable; MSS = microsatellite stable; NCI = National Cancer Institute; ORR = Objective Response Rate; OS = Overall Survival; PD = Pharmacodynamics; PD -L1 = Programmed Cell Death Protein Ligand 1; PFS = Progression free Survival; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; R2PD = recommended Phase 2 dose.

Phase 2	
Primary	
Study Objectives	**Study Endpoints**
• To evaluate the anti-tumor activity of NC410 in combination with Pembrolizumab in Phase 2	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR) based on RECIST v1.1 as assessed by the investigator
Secondary	

Study Objectives	Study Endpoints
• To evaluate the clinical benefit of NC410 in combination with Pembrolizumab in Phase 2	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Duration of Response (DoR), Disease Control Rate (DCR) and Progression-free Survival (PFS) based on RECIST v1.1 as assessed by the investigator b. Overall Survival (OS)
• To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profile of NC410 when combined with Pembrolizumab	• Assessment of PK of NC410 concentration in serum, as well as assessment of combination treatment on the PK/PD profile
• Continue to evaluate the safety and tolerability of NC410 in combination with Pembrolizumab	• Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). Note: Toxicity grading per NCI CTCAE v5.0
Exploratory	
Study Objectives	**Study Endpoints**
• To assess the immunogenicity of NC410 when combined with Pembrolizumab	• Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC410 will be determined
• To evaluate efficacy using iRECIST for immune-based therapeutics	• Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: a. Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on iRECIST as assessed by the investigator
• To explore biomarkers that may predict the pharmacologic activity of NC410 when combined with Pembrolizumab	• Biomarker effects of NC410 in combination with Pembrolizumab in peripheral blood and tumor tissue will be assessed, including but not limited to the following: a. Whole blood immune cell population profiling/immunophenotyping b. Serum markers of inflammation or immune modulation (cytokine & chemokine levels) c. Soluble LAIR-1, LAIR-2 and C1q levels d. Collagen derived products including, but not limited to, C4G, Pro-C3, Pro-C6, etc. e. Tumor biopsy analyses to evaluate the tumor microenvironment in tumor tissue and immune cell infiltrates at baseline and following treatment, and

	correlate expression levels with efficacy including, but not limited to, MSI or MSS status, PD-L1 expression LAIR-1 and collagen staining. f. The expression of additional histological biomarkers may also be assessed based on emerging data
• To characterize the effect on markers of immunity of NC410 when combined with Pembrolizumab	• The effect on markers of immunity may be explored as determined based on emerging data of NC410 in combination with Pembrolizumab

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCR = Disease Control Rate; DoR = Duration of Response; LAIR = Leukocyte-Associated Immunoglobulin-like Receptor;; NCI = National Cancer Institute; ORR = Objective Response Rate; OS = Overall Survival; PD = Pharmacodynamics; PD -L1 = Programmed Cell Death Protein Ligand 1; PFS = Progression free Survival; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

3.1. Description and Duration

This is an open-label, non-randomized, Phase 1b/2 study to determine the safety and tolerability of NC410 when combined with a standard dose of Pembrolizumab. This study will also assess the clinical benefit of combination therapy in participants with advanced unresectable and/or metastatic ICI refractory solid tumors OR ICI naïve MSS/MSI-low solid tumors. Participants will receive Pembrolizumab on Day 1 of each 42-day cycle followed by administration of NC410. Additional doses of NC410 will be given on Day 15 and Day 29 of each 42-day cycle.

The study will be conducted in 2 parts:

- **Phase 1b** – Dose Escalation of NC410 to determine the optimal dose administration schedule and RP2D when combined with a standard dose of Pembrolizumab.
- **Phase 2** – Dose Expansion to evaluate the recommended Phase 2 dose (RP2D) of NC410 in combination with a standard dose of Pembrolizumab.

Participants will continue until progressive disease, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant receives 18 treatments (approximately 2 years) of Pembrolizumab, or administrative reasons requiring cessation of treatment. Note: In the event NC410 is discontinued due to toxicity, continued treatment with pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Participants who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until progressive disease, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed for overall survival (OS) until death, withdrawal of consent, or the end of the study. After the end of treatment, each participant will be followed for 30 days for AE monitoring. Serious adverse events (SAE) and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier.

3.2. Study Phases

3.2.1. Phase 1b – Dose Escalation of NC410 + Pembrolizumab

The Phase 1b portion of the study will enroll participants with advanced unresectable and/or metastatic solid tumors including CRC (without liver metastasis), Gastric including GE junction, Esophageal, Ovarian, and H&N cancers regardless of prior treatment with ICIs or MSS/MSI status (Figure 5). At the sponsors discretion, the expansion of dose level cohorts may be limited to participants with specific tumor types.

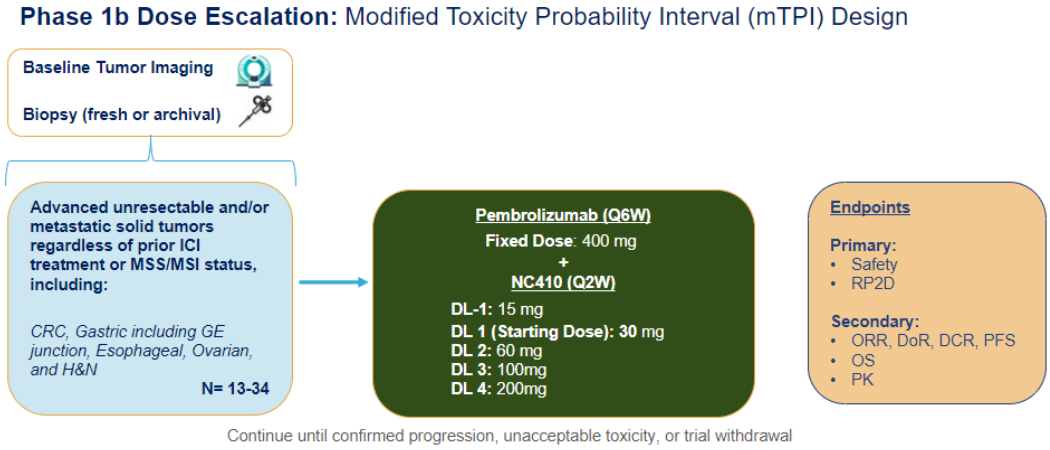
A modified Toxicity Probability Interval (mTPI) (Ji, 2013) with a target dose limiting toxicity (DLT) rate of approximately 30% will be applied for dose escalation and confirmation to determine a recommended Phase 2 dose (RP2D) for NC410 in combination with Pembrolizumab. There will be three dose levels of NC410 evaluated during the Phase 1b portion of the study. The pre-

determined dose levels of NC410 (in combination with a fixed dose of Pembrolizumab of 400mg) will be explored independently.

The dose levels are as follows:

- **Dose Level -1 (de-escalating dose):** 15 mg
- **Dose Level 1 (starting dose):** 30 mg
- **Dose Level 2:** 60 mg
- **Dose Level 3:** 100mg
- **Dose Level 4:** 200mg

Figure 5: Phase 1b Study Design



Abbreviations: CRC = colorectal cancer; DCR = Disease Control Rate; DoR = Duration of Response; GE = gastroesophageal; H&N = head and neck; MSI = microsatellite instable; MSS = microsatellite stable; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression-Free Survival; PK = pharmacokinetics; Q2W = every 2 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 Dose.

The starting dose will be 30mg (Dose Level 1) of NC410. A de-escalation dose of NC410 is available if the starting dose of NC410 is deemed not tolerable in combination with Pembrolizumab. All dose escalation and de-escalation decisions will be based on the occurrence of DLTs at a given dose during the first 42-day period (i.e., Cycle 1) also referred to as the DLT observation period and will be made jointly by the investigators and the sponsor. The dose of Pembrolizumab will remain constant at 400 mg Q6W for each dose level for NC410 and in each cohort through Phase 2.

In Figure 6, the number of participants treated is indicated in the columns and the number of participants who experienced a DLT is indicated in the rows. Dosing decisions include: escalate to the next higher dose (E), stay at the current dose (S), de-escalate to the next lower dose (D), and de-escalate to a lower dose and never test this dose again (i.e., unacceptably toxic dose; DU). Alternative dose levels or administration schedules may be considered pending safety review and emerging data.

Beginning with the starting dose level of NC410 (in combination with a fixed dose of Pembrolizumab), a minimum of 3 evaluable participants will be enrolled. A participant is considered evaluable if they have received 1) at least 1 dose of Pembrolizumab, 2) at least 1 dose of NC410, and 3) completed the 42-day DLT observation period. During dose escalation, a minimum of 3 participants are required at each dose prior to any dose escalation decisions being determined. Depending on accrual rate and occurrence of DLTs, additional participants (up to 10) may be enrolled at each dose cohort until the last of those participants completes the 42-day DLT observation period (i.e., Cycle 1).

For example, the dose escalation rules will proceed as follows if 3 participants are enrolled: if 0 out of the first 3 participants at a given dose level develops a DLT, then the dose can be escalated with the next available participant enrolled to the next level cohort without further expansion. If 1 out of the first 3 participants at a given dose level develops a DLT, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This dose would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (i.e., 4 out of 6 participants). If 2 out of the first 3 participants at a given dose level develop a DLT, the dose will be de-escalated to the lower dose level cohort. If 3 out of the first 3 participants at a given dose level develop a DLT, this dose will be considered unacceptably toxic (i.e., the dose will be de-escalated and never re-escalated to that dose again). The same principle will be applied whether 3, 4, 5 or 6 participants are enrolled in the same dose cohort according to Figure 6.

Based on the mTPI design, the number of participants who are enrolled at a dose, but are not yet fully evaluable for DLT assessment, may not exceed the number of remaining participants who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Figure 6). To determine how many more participants can be enrolled at a dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. In total, 3 to 14 participants may be enrolled at a given dose level during dose escalation.

During or after the completion of Dose Escalation, based on the totality of available data, one or more dose levels may be backfilled/expanded for additional safety, PK, and pharmacodynamic analyses for the purpose of dose optimization. All participants in backfill/dose expansion will be evaluated for DLTs, and the doses will be monitored for additional DLTs, and emerging safety issues.

Dose escalation and confirmation will end after at least 10 evaluable participants have been treated at any of the selected doses. The pool-adjacent-violators-algorithm (Ji, 2013) will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary maximum tolerated dose (MTD). The totality of the data will be considered before a dose is selected to carry forward to Phase 2 and the escalation schedule may be adjusted based on PK, PD, and safety data emerging throughout the study to determine the RP2D. Note that while 30% was the target toxicity rate used to generate the guidelines in Figure 6, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%. If a participant is not evaluable for the DLT observation period for any reason, they may be replaced with the next available participant if escalation or de-escalation rules have not been fulfilled.

The dose level cohort which is determined to be the RP2D will be expanded until at least 10 participants have been dosed and observed for the duration of the 42-day DLT Observation period before moving onto Phase 2 Dose Expansion.

Figure 6: Dose-Finding Rules per Modified Toxicity Probability Interval Design

	Number of Participants Evaluable for DLT at Current Dose											
Number of participants with at least 1 DLT	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU
E = Escalate to the next higher dose; S = Stay at the current dose; D = De-escalate to the next lower dose; DU = The current dose is unacceptably toxic. Target toxicity rate = 30% Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03												

Abbreviation: DLT = Dose-Limiting Toxicity.

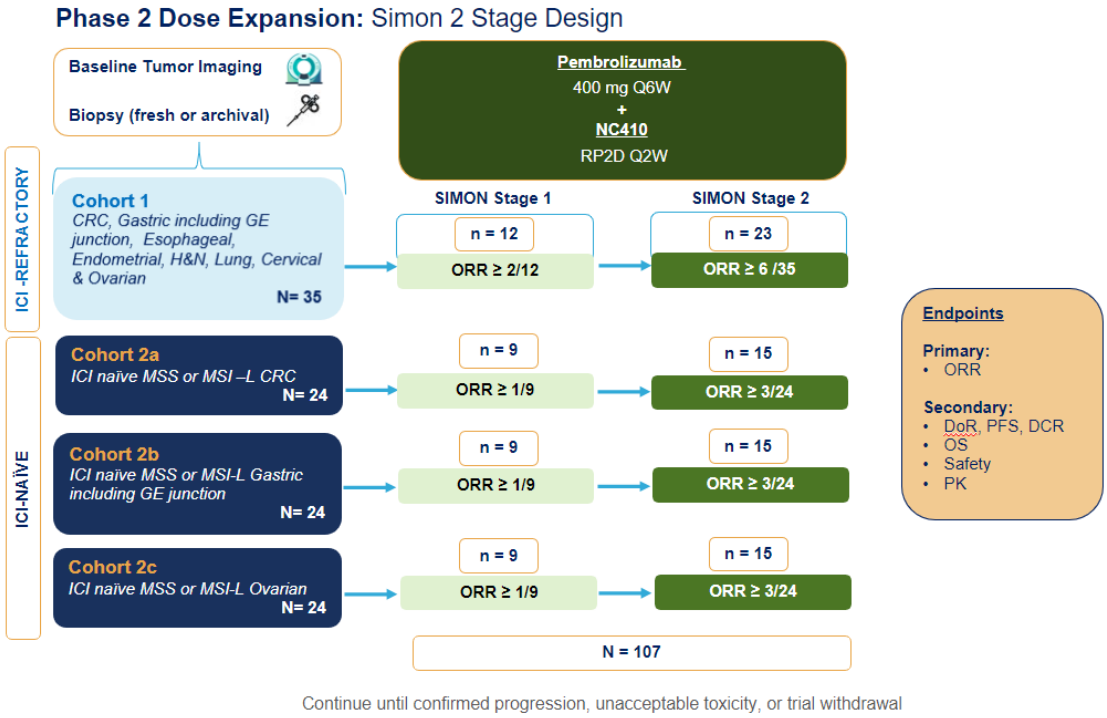
3.2.2. Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the clinical benefit of the RP2D of NC410 in combination with standard dose Pembrolizumab in participants with advanced unresectable and/or metastatic solid tumors across different cohorts as outlined below based on previous ICI refractory or naïve history (Figure 7).

The study will enroll ICI Refractory solid tumors in Cohort 1 and ICI Naïve solid tumors in Cohorts 2a, 2b, and 2c as described below. MSS or MSI-L status must be confirmed prior to entry into these cohorts (either by historical results or during screening).

- **Cohort 1:** ICI Refractory Solid Tumors (CRC MSI-H, Gastric including GE junction, Esophageal, Endometrial, H&N, Lung, Cervical and Ovarian cancer).
- **Cohort 2a:** ICI Naïve MSS or MSI-L CRC
- **Cohort 2b:** ICI Naïve MSS or MSI -L Gastric including GE junction
- **Cohort 2c:** ICI Naïve MSS or MSI-L Ovarian

Figure 7: Phase 2 Study Design



Abbreviations: CRC = colorectal cancer; DCR = Disease Control Rate; DoR = Duration of Response; GE = gastroesophageal; H&N = head and neck; ICI = Immune Checkpoint Inhibitor; ORR = Objective Response Rate per RECIST v1.1; OS = Overall Survival; PFS = Progression-Free Survival; PK = pharmacokinetics; Q2W = every 2 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 Dose.

For the ICI-Naïve group, each cancer type will be considered its own cohort. **Note**: For Cohorts 2a, 2b and 2c, the cancer types were selected based on their anticipated MSS/MSI-L status (approximately 90-95%) across these tumor types. MSS or MSI-L status must be confirmed prior to entry into cohorts 2a, 2b, and 2c (either by historical result or during screening). MSI-H CRC or Gastric including GE junction who have been treated with ICI and become refractory to ICI will be enrolled into Cohort 1 (ICI refractory Solid Tumors).

An optimal 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. For Cohort 1, 12 evaluable participants will be enrolled in the cohort in Stage 1; if 1 or fewer responses are observed within the cohort, then the cohort will be discontinued. If at least 2 responses are observed, 23 additional evaluable participants will be enrolled in the cohort (Stage 2), for at least 35 total evaluable participants in the cohort. For Cohorts 2a, 2b, and 2c, 9 evaluable participants will be enrolled in each of the cohorts in Stage 1; if no response is observed within the cohort, then the cohort will be discontinued. If at least 1 response is observed, 15 additional evaluable participants will be enrolled in the cohort (Stage 2), for at least 24 total evaluable participants per cohort.

3.3. Measures Taken to Avoid Bias

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

3.4. Number of Participants

3.4.1. Planned Number of Participants

Overall, study accrual will be approximately 209 participants. This includes approximately 102 participants enrolled in Phase 1b safety expansion portion of the study, followed by approximately 107 participants enrolled in Phase 2 dose expansion. Additional subjects, with tumor types of interest, may be enrolled at 1 or more dose levels to allow for dose optimization prior to selecting a recommended Phase 2 dose (RP2D).

3.4.2. Replacement of Participants

Participants may be replaced for any of the following reasons:

- In Phase 1b, any participant who withdraws from treatment before the completion of the DLT period (42-days) for any reason other than a DLT (e.g., participant is not evaluable for DLTs)
- In Phase 1b and Phase 2, a participant who has not met the biopsy requirements for the study (i.e. archival or fresh at pre-treatment) may not be eligible to enroll. **Note**: If a participant is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the participant may still enroll in the study.
- Participant does not meet the eligibility requirements of the study (accidental enrollment)

3.5. Duration of Treatment and Participation

After signing the informed consent form (ICF), screening assessments may be completed over a period of approximately 30 days. Participants will continue until progressive disease, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant receives 18 treatments (approximately 2 years) of Pembrolizumab, or administrative reasons requiring cessation of treatment. **Note**: In the event NC410 is discontinued due to toxicity, continued treatment with pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

3.6. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study will occur when all participants have completed the last study follow-up visit or have discontinued study drug and have completed applicable follow-up assessments. Participants may be eligible to receive study treatment for up to 2 years or until criteria for discontinuation of treatment is met (whichever comes first).

The end of the study may be declared when no more than 5 participants remain on study treatment for at least 6 months, at which point a database lock of the study may occur to allow for analysis of the study data. Any remaining participants may continue to receive study treatment and be seen by the investigator per standard of care until withdrawal criteria is met (Section 5.10). The investigator will be expected to monitor for and report any serious AEs (SAEs), ECI, overdoses, and pregnancies, as detailed in Sections 9.1, 9.1.3, and 9.4. The remaining participants will be considered on study until a discontinuation criterion is met and written notification is provided to the sponsor.

3.7. Continued Access

Participants who are still on study intervention at the time of study completion/termination may continue to receive study intervention if they are experiencing clinical benefit. The continued access to study intervention will end when a criterion for discontinuation is met or 18 doses of pembrolizumab have been administered.

3.8. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The (IRB)/independent ethics committee (IEC) must be notified in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain one copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision or upon review of emerging data. If the study is terminated prematurely, then the sponsor or designee will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

4. PARTICIPANT ELIGIBILITY

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

4.1. Participant Inclusion Criteria

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

1) The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
2) Be ≥ 18 years of age on day of signing informed consent.
3) Participant with histologically or cytologically confirmed diagnosis of the following advanced unresectable and/or metastatic solid tumors:
    a. **Phase 1b:** Participants with solid tumors that are known to be associated with MSS/MSI-low in the majority including: CRC (liver metastasis negative), Gastric including GE junction, Esophageal, Ovarian, and H&N cancer (regardless of prior treatment with ICIs).

        Note: Participants must have had disease progression after at least one line of systemic standard of care therapy prior to enrollment. Participants who discontinue standard treatment due to intolerance or refuse standard treatment will also be eligible to enroll.

    b. **Phase 2 ICI Refractory (Cohort 1):**
        i. Participants with solid tumors including CRC, Gastric including GE junction, Esophageal, Endometrial, H&N, Lung, Cervical and Ovarian cancer.
        ii. Participants must have progressed on treatment with an anti-PD1/L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting <u>all of the following criteria</u>:
            1. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.
            2. Has demonstrated disease progression after PD-1/L1 as defined by RECIST v1.1.

    c. **Phase 2 ICI naïve (Cohorts 2a-2c):**
        i. Tumors known to be associated with MSS/MSI-low status such as CRC, Gastric including GE junction, and Ovarian where participants have not been previously treated with ICIs.

            Note: Participants must have had disease progression after at least one line of systemic standard of care therapy prior to enrollment. Participants who discontinue standard treatment due to intolerance or refuse standard treatment will also be eligible to enroll.

Note: Confirmation of MSS/MSI status should be assessed prior to study entry (either by historical result or during screening).

4) A male participant must agree to use contraception and refrain from sperm donation or expecting to father a child, from Screening through the treatment period and for at least 120 days after the last dose of study treatment.

5) A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP)

    b. A WOCBP who agrees to follow contraceptive guidance outlined in Section 6.2 from Screening through the treatment period and for at least 120 days after the last dose of study treatment.

6) Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

7) Able to provide tumor tissue sample at Screening, archival (≤ 5 years old) or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. If a tumor block is unavailable, a minimum of 8 unstained slides may be submitted.

    Note: If a participant is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the participant may still enroll in the study.

8) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

9) Life expectancy greater than or equal to 12 weeks as judged by the Investigator.

10) Have adequate organ function as defined in the following table (Table 1). Specimens below must be collected within 10 days prior to the start of study treatment (i.e. C1D1).

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

[1] Criteria must be met without packed red blood cell (PRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

[2] Creatinine clearance (CrCl) should be calculated per institutional standard.

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

Note: Participants with liver metastases at baseline may be inviting DLTs and labs should be reviewed and discussed with the medical monitor prior to initial dosing.

4.2. Participant Exclusion Criteria

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

Medical Conditions

Pregnancy Exclusion

1) A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

2) Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137), and was discontinued from that treatment due to a Grade 3 or higher irAE.

3) Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (could consider shorter interval for kinase inhibitors or other short half-life drugs) prior to treatment.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤ 2 requiring treatment or hormone replacement may be eligible.

   Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.

4) Has received prior radiotherapy within 2 weeks of start of study treatment or has had a history of radiation pneumonitis.

   Note: Participants must have recovered from all radiation-related toxicities and do not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

5) Has received G-CSF or GM-CSF within 7 days prior to start of study treatment.

6) Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention.

   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

7) Receipt of COVID-19 vaccine within ≤ 14 days prior to first administration of study treatments.

   Note: For 2-dose COVID-19 vaccines or COVID-19 booster, participants must wait at least 14-days after administration prior to beginning study treatment.

Prior/Concurrent Clinical Study Experience

8) Receipt of an investigational agent or use of an investigational device within 4 weeks prior to the first dose of study treatment.

9) Has had an allogeneic tissue/stem cell/solid organ transplant.

Diagnostic assessments

10) Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

11) Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of bladder, that have undergone potentially curative therapy are not excluded.

12) Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

13) Has severe hypersensitivity (≥ Grade 3), known allergy or reaction to Pembrolizumab, NC410, and/or any of their excipients.

14) Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

15) Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.

16) Has an active infection requiring systemic therapy.

17) Has known active or history of HIV infection. No HIV testing is required unless mandated by local health authority.

18) Has known active Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Participant Numbering and Treatment Assignment

All eligible participants, after signing the ICF, will be allocated by non-random assignment, and will receive a unique participant number with the first 4 digits serving as the site number. The participant numbering will be managed by the sites.

Investigative sites must complete all applicable CRFs for participants consented to the trial, even if the participant is not treated with study drug (i.e., screen failure).

Dose level and cohort assignment will occur at time of participant 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 participants will be assigned to a cohort to receive NC410 in combination with pembrolizumab; 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. Trial Treatment

Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen	Sourcing
KEYTRUDA© (Pembrolizumab)	Solution for infusion	100 mg/vial	400 mg Q6W	IV infusion	Day 1 of each 42-day cycle	Provided by Sponsor
NC410	Solution for infusion	320mg/vial	RP2D Q2W	IV infusion	Day 1, Day 15 and Day 29 of each 42-day cycle	Provided by Sponsor

Abbreviations: IV = intravenous; Q2W = every 2 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 Dose.

5.3. Description and Administration

5.3.1. NC410 Description and Administration

NC410 is in frozen liquid form formulated for iv infusion. The drug product is provided in a 20 mg/mL (320 mg/vial) concentration. The drug can be diluted as low as 0.04 mg/mL; additional information can be found in the NC410 IB. The infusion site should not be used for blood sampling.

NC410 will be administered on Day 1 of each 6-week (42-day) treatment cycle, 30-60 minutes after the administration of pembrolizumab. NC410 will also be administered on Day 15 and Day 29 of each treatment cycle, as a stand-alone infusion.

The NC410 Pharmacy Manual contains specific instructions for the preparation of the NC410 infusion and administration of infusion solution.

5.3.2. KEYTRUDA© (Pembrolizumab) Description and Administration

Pembrolizumab will be administered using IV infusion on Day 1 of each 6-week (42-day) treatment cycle after all procedures and assessments have been completed.

Pembrolizumab will be administered as a dose of 400 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

The pembrolizumab Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

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.

5.4. Supply Packaging and Labeling

5.4.1. NC410 Supply Packaging and Labeling

NC410 will be supplied as 16mL aqueous solution in 20 mL glass vials with 20 mg/mL of NC410. Study drug will be packaged as open-labeled supplies, each vial will be labeled and placed in a carton. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of NC410.

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.

5.4.2. KEYTRUDA© (pembrolizumab) Supply Packaging and Labeling

Pembrolizumab will be supplied as a 4mL aqueous solution in 10mL glass vials with 25mg/mL of pembrolizumab. Study drug will be packaged as open-label supplies, each vial labeled and placed in a carton. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of pembrolizumab.

5.5. Storage

5.5.1. NC410 Storage

NC410 must be stored in a -20°C freezer, protected from light, in a secure, controlled-access location. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Study drug may not be used for any purpose other than that stated in the protocol. The NC410 Pharmacy Manual contains additional information regarding storage of study drug.

5.5.2. Pembrolizumab Storage

KEYTRUDA© (Pembrolizumab) must be stored in a refrigerator (2-8°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.

5.6. Accountability

Detailed information such as requirements for accountability and disposal of study drug can be located within the NC410 and KEYTRUDA© (pembrolizumab) pharmacy manuals, which will be provided separately.

5.7. Treatment Compliance

Compliance with NC410 and pembrolizumab 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.

5.8. Dose Modifications

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

Treatment with NC410 in combination with pembrolizumab may be delayed allowing for resolution of toxicities. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study.

An NC410 infusion should generally not be delayed greater than 28-days between sequential doses. If a dose of NC410 is missed, the participant should remain on the original treatment schedule and NC410 should be administered at the time of next planned dose. If a participant misses two or more subsequent doses of NC410, the Sponsor should be notified immediately to discuss participant treatment schedule and determine next steps.

Note: Exceptions will apply for delay in dosing during Phase 1b, as detailed in the DLT criteria under Section 5.9.

Study Treatment (defined as NC410 + Pembrolizumab) may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). However, study intervention is to be restarted within 6 weeks or 42 days of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor.

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

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

5.8.2. Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab and NC410

AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds (i.e. NC410)_ may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 2.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to NC410 alone, or to pembrolizumab alone, for adverse events listed in Table 2, both interventions must be held according to the criteria in Table 2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions*:*

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 2.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

If the toxicities do resolve and conditions are aligned with what is defined in Table 2, the combination of NC410 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to NC410 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Table 2: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General instructions: Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.				
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie. peritoneal signs and ileus) Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM	Monitor participants for hyperglycemia or other signs and symptoms of diabetes

General instructions:
Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
			Administer antihyperglycemic in participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

General instructions:
Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Abbreviations: AE(s) = adverse event(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE =Common Terminology Criteria for Adverse Events; DRESS = Drug Rash with Eosinophilia and Systemic Symptom; GI = gastrointestinal; IO = immuno-oncology; ir = immune related; IV = intravenous; SJS = Stevens-Johnson Syndrome; T1DM = type 1 diabetes mellitus; TEN = Toxic Epidermal Necrolysis; ULN = upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.
[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal
[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal
[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (e.g., vasculitis and sclerosing cholangitis).

5.8.3. Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab or NC410

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab and NC410 associated infusion reaction are provided in Table 3.

Table 3: Infusion Reaction Dose Modification and Treatment Guidelines (Pembrolizumab or NC410)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h our (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

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

5.9. Dose Limiting Toxicities (DLTs) During Phase 1b

5.9.1. 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 42 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 4, except for events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.

Individual participant dose reductions may be made based on events observed at any time during treatment with NC410+pembrolizumab; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the RP2D of NC410 in combination with pembrolizumab, decisions will be made based on events that are observed from the first day of study treatment through and including the 42-day DLT period. Alternative dose levels may

subsequently be determined based on relevant toxicities that become evident after the 42-day DLT period.

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study treatment administration.

Table 4: Definition of Dose-Limiting Toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

Nonhematologic toxicity
• Any Grade 3 or Grade 4 non-hematologic laboratory value if: o Clinically significant medical intervention is required to treat the participant or o The abnormality leads to hospitalization, or o The abnormality persists for >1 week. o The abnormality results in a Drug-induced Liver Injury (DILI) **Exceptions**: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc. • Any nonhematologic AE ≥ Grade 3 in severity should be considered a DLT, with the following exceptions: o Grade 3 fatigue lasting ≤ 3 days o Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheal per standard of care o Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
Hematologic toxicity
• Grade 4 hematologic toxicity lasting ≥7 days, except for thrombocytopenia: o Grade 3 thrombocytopenia with clinically significant bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent medical intervention). o Grade 4 thrombocytopenia of any duration. • Febrile neutropenia Grade 3 or Grade 4: o Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour o Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated
General
• Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity. • Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1. • Missing >25% of NC410 doses as a result of drug-related AE(s) during the first cycle. • Grade 5 toxicity. • Any death not clearly due to the underlying disease or extraneous causes.

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

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

5.9.3. Follow-Up of Dose-Limiting Toxicities

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

5.9.4. Procedures for Cohort Review and Dose Finding in Phase 1b

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 finding, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

5.10. Withdrawal/Discontinuation of Participants from Study Treatment

5.10.1. Withdrawal/Discontinuation Criteria

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

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

If a participant 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).

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

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

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

- Consent is withdrawn for treatment (agrees to follow-up)
- The participant becomes pregnant
- Confirmed radiographic progressive disease

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or deriving clinical benefit. See Section 8.7

- Unacceptable adverse experiences as described in Section 9
- Investigator's decision to withdraw participant
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 4 cycles (at least 24 weeks), receiving 1 cycle of the combination including 1 dose of pembrolizumab and at least 2 of the planned doses of NC410 beyond the date when the initial CR was declared.
- Completion of 18 administrations (approximately 2 years) with pembrolizumab

  Note: The number of administrations is calculated starting with the first dose of pembrolizumab.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.8.
- The study is terminated by the IRB or regulatory authority
- The study is terminated by the sponsor

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

5.10.2. Withdrawal Procedures

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

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

5.11. Concomitant Therapy

5.11.1. Prior and Concomitant Medications Review

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

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 participant's primary physician. However, the decision to continue the participant on study drug or vaccination schedule requires the agreement of the investigator, the sponsor, and the participant.

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or NC410
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

  Note: Palliative radiation during the treatment period of this study is allowed with the exception to target lesions.

- Live or live attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Note: Killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

- COVID-19 vaccine within 14 days prior to receiving the first dose of study drug and during the 42-day DLT period.

  Note: For 2-dose COVID-19 vaccines and/or booster, participants must wait at least 14-days after 2nd vaccine dose administration.

- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat COPD exacerbations (only short-term oral or IV use in doses >10mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
  - Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

    Note: Inhaled steroids are allowed for management of asthma.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, all study treatments (NC410 & Pembrolizumab) must be discontinued.

5.11.2. Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.8.2.

Note: If after the evaluation of the event, it is determined not to be related to study treatment, the investigator does not need to follow the treatment guidance. Refer to Table 2 in Section 5.8.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6. DIET/ACTIVITY/OTHER CONSIDERATIONS

6.1. Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.2. Contraception

NC410 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male participants will be considered to be of **non-reproductive potential** if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female participants will be considered of **non-reproductive potential** if they are either:

1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

   OR

2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

   OR

3) Has a congenital or acquired condition that prevents childbearing.

Female and male participants of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

1) practice abstinence† from heterosexual activity;

   OR

2) use (or have their partner use) acceptable contraception during heterosexual activity

Acceptable methods of contraception are‡:

<u>Single method (one of the following is acceptable):</u>

- Intrauterine device (IUD)
- Vasectomy of a female participant's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous
- Contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the participant's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for participants participating at sites in this country/region.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

For countries or sites that follow the Clinical Trial Facilitation Group (CTFG) guidance, please use the following:

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if these therapies have transient adverse effects on the composition of sperm. Therefore, nonpregnant, non-breastfeeding women may only be enrolled if they are willing to follow the CTFG Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Participants should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Participants should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

6.3. Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with NC410 in combination with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

6.4. Use in Nursing Women

It is unknown whether pembrolizumab or NC410 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

7. SCHEDULE OF STUDY PROCEDURES

Table 5: Schedule of Assessments

Trial Period	Protocol Section	Screening Phase	Treatment[b]										Post-Treatment		
			Cycles 1 & 2 Only						All Other Cycles (42 days)			Every 9 weeks	End of Treatment (EOT)	Disease Status Follow-Up[ff]	Survival Follow-Up[gg]
Visit Day		Screening	Day 1	Day 2	Day 8 (Cycle 1 Only)	Day 15	Day 16	Day 29	Day 1	Day 15	Day 29	Disease Status	Upon discontinuation of study treatment	*If EOT for reason other than progressive disease*	Every 9 weeks
Scheduling Window (Days)		~ 30 Days	± 3 days *(after Cycle 1)*		± 1 day	± 3 days		± 3 days	± 3 days	± 3 days	± 3 days	± 7 days		Every 9 weeks	
ADMINISTRATIVE PROCEDURES															
Informed consent[a]	8.1	X													
Eligibility (I/E) criteria	4	X													
Demographics	8.3.1	X													
Medical History[e]	8.3.1	X													
Cancer History and Diagnosis	8.3.2	X													
Prior/Concomitant Medications[f]	8.4	X													
Post-study anti-cancer therapy	8.5												X		X
Survival Status[hh]	7.4.3		<----------X---------->												X
CLINICAL PROCEDURES/ASSESSMENTS															
Administer NC410[c]	5.3.1		X[c]			X[c]		X[c]	X[c]	X[c]	X[c]				
Administer Pembrolizumab[d]	5.3.2		X[d]						X[d]						
Comprehensive PE[g]	8.6.2.1	X[g]											X[g]		
Targeted physical assessment[h]	8.6.2.2		X[h]		X[h]	X[h]		X[h]	X[h]	X[h]	X[h]				
Vital signs and weight[i]	8.6.4	X	X			X		X	X	X	X		X		
Height	8.6.4	X													
ECOG performance	8.6.3	X	X		X	X		X	X	X	X		X		
12-lead ECG[j]	8.6.5	X[j]													

Trial Period	Protocol Section	Screening Phase	Treatment[b]										Post-Treatment		
			Cycles 1 & 2 Only						All Other Cycles (42 days)			Every 9 weeks	End of Treatment (EOT)	Disease Status Follow-Up[ff]	Survival Follow-Up[gg]
Visit Day		**Screening**	**Day 1**	**Day 2**	**Day 8 (Cycle 1 Only)**	**Day 15**	**Day 16**	**Day 29**	**Day 1**	**Day 15**	**Day 29**	**Disease Status**	**Upon discontinuation of study treatment**	***If EOT for reason other than progressive disease***	**Every 9 weeks**
Scheduling Window (Days)		**~ 30 Days**	**± 3 days *(after Cycle 1)***		**± 1 day**	**± 3 days**		**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**		**Every 9 weeks**	
AE assessment[k]	9.1	X													
LOCAL SAFETY LAB ASSESSMENTS[l, d]															
Hematology with differential	Table 6	X[l]	X[m]			X		X	X[n]	X	X		X		
Comprehensive Serum Chemistries	Table 6	X[l]	X[m]			X		X	X[n]	X	X		X		
Coagulation panel	Table 6	X[l]													
Urinalysis[o]	Table 6	X[l]													
Endocrine function test[p]	Table 6	X[l]	X[m]						X[n]						
Complement Test (CH50)[s]	Table 6		X[s]			X[s]		X[s]							
Serum Tumor Markers[hh]	Table 6	X	X						X						
Hepatitis B and C (if indicated)[l]	Table 6	X[l]													
Serum Pregnancy Test	Table 6	X[q]											X		
Urine Pregnancy Test[r]	Table 6		X			X		X	X[n]	X	X				
CENTRAL LAB ASSESSMENTS															
Pharmacokinetics (PK)[t]	Table 7		X[t]	X[t]	X[t]	X[t]			X[t]						
Anti-Drug Antibodies (ADA)[u]	Table 7		X[u]						X[u]				X[u]		
Immunophenotyping	Table 7		X[v]			X[v]		X[v]							
Cytokines[w,x]	Table 7		X[w,x]	X[w,x]	X[w]	X[w,x]	X[w,x]								
Plasma ctDNA[y]	Table 7		X [(Cycle 1 only)]												
Tumor Biopsy	8.9.1	X[bb]	A tumor biopsy should be performed at Week 8 (± 3 days)[z]										X[aa]		
EFFICACY MEASUREMENTS															
Radiologic assessments	8.7	X[cc]	The first on treatment tumor assessment should be performed at Week 9 (± 7 days)[dd]									X[dd]	X[ee]	X[ff]	

a. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 10 days prior to the first dose of trial treatment).
b. Treatment cycles will begin every 42 days (± 3 days after Cycle 1).
c. NC410 will be administered every 2 weeks at Day 1, Day 15 and Day 29 of each treatment cycle. On Day 1 of each treatment cycle NC410 will be administered 30-60 minutes AFTER the end of the pembrolizumab iv infusion.
d. Keytruda© (Pembrolizumab) will be administered every 6 weeks on Day 1 of each treatment.
e. Medical history will include relevant medical or surgical treatment within the last 10 years considered to be clinically significant by the investigator.
f. Any prior medication received up to 30 days before the first dose of study drug should be recorded. All concomitant medications received up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. Please also refer to Sections 5.11.1 and 5.11.2 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.
h. Targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. Notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs or Medical History (if applicable at Screening).
i. During Cycle 1, participants will be required to stay at the study site for safety observation for 2 hours after administration of NC410 infusion, on Days 1, 15, and 29. During Cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose of first study treatment, at the end of infusion of study treatment, and every 60 minutes ± 10 minutes thereafter for 2 hours. For all subsequent cycles participants will be required to be observed for 1 hour post end of infusion of study treatment or per PI discretion. At subsequent cycles, vital signs will be assessed pre-dose of first study treatment and at the end of infusion (+10 minutes) of study treatment. Additional vital signs may be collected per PI's discretion if indicated. Participants will also be assessed for the onset of acute AEs.
j. A standard 12-lead electrocardiogram (ECG) will be performed one time during screening using local standard procedures. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary at the discretion of PI.
k. All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before first study treatment must be reported by the investigator if they cause the participant to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure. From the time of first study treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. SAEs and ECIs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier.
l. Safety Lab assessment required analytes are in Table 6. Laboratory tests performed during screening to confirm adequate organ function (ANC, Platelets, Hemoglobin, Creatinine OR Measured/Calculated Creatinine Clearance, Total Bilirubin, AST, ALT, INR or PT and aPTT) are to be performed within 10 days prior to the first dose of trial treatment. Note: HBV and HCV tests are only required at screening if participant has a known history of HBV or HCV infection or if testing is mandated by local health authority.
m. Laboratory samples on Cycle 1 Day 1 must be performed before the administration of any study treatment. Safety lab results should be reviewed by the investigator designee and found to be acceptable prior to the administration of study drug.
n. After Cycle 1 Day 1, pre-dose laboratory procedures can be conducted up to 72 hours before administration of study treatment. Safety lab results should be reviewed by the investigator or qualified designee and found to be acceptable before treatment is initiated.
o. Urinalysis to be performed at Screening. Urine dipstick – if abnormal, perform microscopic urinalysis.
p. Endocrine function tests are required every 6 weeks and should be performed prior to pembrolizumab dosing on Day 1 of each cycle.
q. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study drug.
r. For women of child-bearing potential only, Day 1, 15 and 29 urine pregnancy must be performed within 72 hours prior to study treatment and resulted before study drug administration. If positive, confirm results with serum pregnancy test.
s. CH50 will be collected pre-Pembrolizumab infusion and post-NC410 infusion (+ 10-15 minutes) at Day 1 followed by pre-and post-NC410 infusion (post-infusion + 10-15 minutes) on Day 15 and Day 29 of Cycles 1 & 2 only. After Cycle 2, Complement tests may be performed locally if medically indicated per PI discretion.
t. PK will be collected pre-Pembrolizumab infusion and 30 minutes post-NC410 infusion on Day 1 of Cycles 1, 2, 3, 5, 7 and 9. Additionally, PK will be collected at Day 2, Day 8 and Day 15 during Cycle 1 only.
u. ADA will be collected pre-Pembrolizumab infusion on Day 1 of Cycles 1, 2, 3, 5, 7 and 9 and at End of Treatment.
v. Immunophenotyping will be collected pre-Pembrolizumab infusion on Days 1, 15 and 29 of Cycles 1 and 2.

w. During Cycle 1 Cytokines will be collected pre-Pembrolizumab infusion on Day 1 and pre-NC410 infusion on Day 15. Additionally, cytokines will be collected at Day 2 (24-hr post NC410 infusion), Day 8 (anytime) and Day 16 (24-hr post NC410 infusion).
x. During Cycle 2 Cytokines will be collected pre-Pembrolizumab infusion on Day 1 and pre-NC410 infusion on Day 15. Additionally, cytokines will be collected at Day 2 and Day 16 (24-hr post NC410 infusion).
y. Plasma ctDNA will be collected pre-Pembrolizumab infusion on Cycle 1 Day 1.
z. On-treatment tumor biopsy should be completed at Week 8 (± 3 days). The tumor biopsy should be performed prior to the first on-study radiologic assessment.
aa. An optional EOT biopsy will be collected for participants who consent for EOT biopsy at time of ICF.
bb. At screening, archived tumor biopsies ≤ 5 years will be acceptable, however a fresh biopsy is preferred. If a participant is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the participant may still enroll in the study after consultation with the medical monitor.
cc. 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 participant throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for participant management.
dd. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from Cycle 1 Day 1 (first dose of study treatments) and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated. Imaging should follow calendar days and should NOT be adjusted for delays in cycle starts. After 1 year of treatment, scans may be performed according to standard of care schedule.
ee. If scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation (EOT) is not mandatory. For participants 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 participants who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status every 9 weeks (63 days ± 7 days) or per standard of care by radiographic imaging until 1) withdrawal of consent, 2) the start of new systemic anti-cancer therapy, 3) documented disease progression, 4) death, or 5) the end of the study, whichever occurs first.
ff. Participants 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 9 weeks (63 days ± 7 days) or per standard of care by radiologic imaging to monitor disease status. The Follow-up Visits should occur approximately every 9 weeks (after treatment discontinuation) to review AEs and post-treatment anti-cancer therapy status. However, to minimize participant burden, if the time window for this visit does not align with the timing for the continued tumor imaging, the first Follow-up Visit may be performed earlier than scheduled to align these two visits. The imaging schedule should not be adjusted.
gg. Participants that experience site assessed progressive disease or start a new anti-cancer therapy should be followed approximately Q9W to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
hh. Serum tumor markers (CEA or CA-125) should be collected locally at Screening and Day 1 of every Cycle until treatment discontinuation; may be collected up to 72 hours prior to the scheduled time point. Type of tumor marker collected is dependent on cancer type. See Section 8.6.6.3 for more information.

Table 6: Local Laboratory Tests: Required Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Hepatitis Screening</th><th>Coagulation</th></tr>
<tr><td rowspan="5">Albumin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Bicarbonate or Carbon[b] dioxide
Blood urea nitrogen/Urea[c]
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td><td rowspan="5">Complete blood count, including:
Hemoglobin
Hematocrit
Platelet count
Red blood cell count
Absolute White blood cell count

Differential count (% and absolute), including:
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils</td><td>Specific gravity
Microscopic Exam[a]
Glucose
Blood
Protein</td><td rowspan="3">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 participant eligibility.</td><td rowspan="3">PT
aPTT
INR</td></tr>
<tr><td>Serum Tumor Markers</td></tr>
<tr><td>Carcinoembryonic Antigen (CEA)
Cancer Antigen 125 (CA-125)</td></tr>
<tr><td>Complement Tests</td><td colspan="2">Pregnancy Testing</td></tr>
<tr><td>Total Hemolytic Complement Test (CH50)</td><td colspan="2" rowspan="2">Female participants of childbearing potential require a serum test at screening and EOT. Urine pregnancy tests will be performed on Day 1 of all other cycles.

Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td></tr>
<tr><td>Endocrine Function Tests[e]</td></tr>
<tr><td>Thyroid-stimulating hormone
Free thyroxine (Free T4)
Total triiodothyronine (Total T3) OR Free triiodothyronine (Free T3)[d]</td><td colspan="2"></td></tr>
</table>

Abbreviations: aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CEA = carcinoembryonic antigen; CH50 = total hemolytic complement test; DNA = deoxyribonucleic acid; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time; RNA = ribonucleic acid; ULN = upper limit of normal; WBC = white blood cell.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
a Microscopic exam required, if abnormal results are noted with urine dipstick
b If these tests are not done as part of standard of care in your region, then these tests do not need to be performed.
c Blood Urea Nitrogen is preferred; if not available urea may be tested.
d T3 is preferred; if not available, free T3 may be tested.
e Endocrine function test are required every 6 weeks, on Day 1 of each cycle
f Tumor-specific marker should be collected based on cancer under study.

Table 7: Schedule of Pharmacokinetic (PK) and Pharmacodynamic (PD) Sampling

Cycle	Visit Day	Assessment	Timing of Sample Collection
Cycle 1	Day 1	PK ADA Immunophenotyping Cytokines Plasma ctDNA	Pre-infusion**
		PK	30 min post- infusion* (+ 10 min)
	Day 2	PK Cytokines	24-hr post- infusion* (+/- 30 min)
	Day 8	PK Cytokines	Anytime
	Day 15	PK Immunophenotyping Cytokines	Pre-infusion**
	Day 16	Cytokines	24-hr post- infusion* (+/- 30 min)
	Day 29	Immunophenotyping	Pre-infusion**
Cycle 2	Day 1	PK ADA Immunophenotyping Cytokines	Pre-infusion**
		PK	30 min post- infusion* (+10 min)
	Day 2	Cytokines	24-hr post- infusion* (+/- 30 min)
	Day 15	Immunophenotyping Cytokines	Pre-infusion**
	Day 16	Cytokines	24-hr post- infusion* (+/- 30 min)
	Day 29	Immunophenotyping	Pre-infusion**
Cycles 3, 5, 7, and 9	Day 1	PK ADA	Pre-infusion**
		PK	30 min post- infusion* (+ 10 min)
End of Treatment		ADA	Untimed ADA sample

Abbreviations: ADA = anti-drug antibody; ctDNA = circulating tumor deoxyribonucleic acid; hr = hours; min = minutes; PK = pharmacokinetics;
* Post -infusion collection timepoints will be calculated from the end of NC410 infusion.
** Pre-infusion collections to occur prior to Pembrolizumab dosing on Day 1 and prior to NC410 infusion on Day 15 and Day 29 of each treatment cycle.

7.1. Screening Period

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (e.g., Cycle 1 Day 1). Screening should be completed over 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 participant '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 participant 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 participant eligibility. Additionally, a participant who fails screening may repeat the screening process **1 time** if the investigator believes there has been a change in eligibility status (e.g., after recovery from an infection). Treatment should start as soon as possible after the date of enrollment.

7.2. Treatment Period

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

Participants will have regularly scheduled study visits on Day 1, Day 15 and Day 29 of every cycle. Additional visits will be required on Day 2, Day 8 and Day 16 of Cycle 1, and Day 2 and Day 16 of Cycle 2. During study visits, the participant will have clinical and laboratory assessments as outlined in the Schedule of Assessments. At certain study visits, participants will have PK, PD, and biomarker samples obtained (see Table 7).

During Cycle 1, participants will be required to stay at the study site for safety observation for 2 hours after administration of NC410 infusion, on Days 1, 15, and 29. For all subsequent cycles participants will be required to be observed for 1 hour post end of infusion of study treatment or per PI discretion. Participants will also be assessed for the onset of acute AEs.

7.3. End of Treatment Visit

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

7.4. Post-Treatment Follow-up

7.4.1. Disease Status Follow-up

Participants 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 9 weeks (63 days ± 7 days) thereafter or per standard of care, by radiologic imaging to monitor disease status.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

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 as defined by RECIST 1.1*
- Pregnancy
- Death
- End of the study

***** Participants who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed when clinically appropriate.

7.4.2. Survival Follow-up

Participants who experience confirmed disease progression (either by RECIST 1.1. or iRECIST) or start a new anti-cancer therapy, will move into the Survival Follow-Up phase and should be contacted by telephone every 9 weeks after End of Treatment to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.4.3. Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Safety Monitoring Board (eDSMB) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the eCRF).

7.5. End of Study (Subject Disposition)

The end of study will occur when all participants have met withdrawal criteria as listed in Section 5.10.1.

7.6. Unscheduled Visits

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

8. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled timepoints if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary for reasons related to participant 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 participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the participant before conducting any study-specific procedures using an ICF approved by the IRB/IEC and/or other regulatory authorities (as required per local laws and regulations). The ICF should contain all elements required by ICH E6 and describe the nature, scope, and possible consequences of the study in a manner that the participant 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 participant. The informed consent process for each participant must be documented in writing within the participant source documentation.

8.2. Participant Identification Card

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

8.3. Demography and Medical History

8.3.1. Demographics and General Medical History

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

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

8.3.2. Disease Characteristics and Prior Anticancer Treatment History

A disease-targeted medical and medication history will be collected at screening. Details regarding the participant 's malignancy under study including but not limited to: date of diagnosis, initial and current cancer stage, primary tumor histology, and prior treatments including systemic, radiation,

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

8.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine participant eligibility. All concomitant medications and procedures must be recorded in the eCRF, and any medication received, or procedure performed within 30 days before the first dose of study drug.

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

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

8.5. Poststudy Anticancer Therapy

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study drug, including any anticancer systemic therapy, radiotherapy, or surgery. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

8.6. Clinical Assessments and Procedures

8.6.1. Adverse Event Monitoring

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

8.6.2. Physical Examinations

8.6.2.1. 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.

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.

8.6.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by participant symptoms, AEs, or other findings. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.6.3. Eastern Cooperative Oncology Group Performance Status

The investigator will assess Eastern Cooperative Oncology Group (ECOG) performance status at Screening, on Day 1, 15, and 29 of each Cycle, and on Day 8 of Cycle 1 (Oken, 1982). More information on assessing performance status using ECOG can be found in Appendix 5.

8.6.4. Height, Weight, and Vital Signs

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

During Cycle 1, participants will be required to stay at the study site for safety observation for 2 hours after administration of NC410 infusion on Days 1, 15, and 29. During Cycle 1, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed pre-dose of first study treatment, at the end of infusion of study treatment, and every 60 minutes ± 10 minutes thereafter for 2 hours.

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

Height will be recorded at Screening only.

8.6.5. 12-Lead Electrocardiogram

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

8.6.6. Local Safety Laboratory Assessments

A laboratory, local to the study site and participant, will perform all clinical laboratory assessments for safety (e.g., blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). All local laboratory assessments should be performed using standard procedures on the days indicated in the Schedule of Assessments (Table 5). Additional information regarding the specific laboratory analytes required for each test are detailed in Table 6. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment on Cycle 1 Day 1 and results should be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of study treatment.

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

8.6.6.1. Pregnancy Testing

A local laboratory serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study drug. Urine pregnancy tests will be performed locally as outlined in Table 5 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 participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

8.6.6.2. Hepatitis Screening Tests

Hepatitis assessments are only required to be performed at screening if participant has a known history of HBV or HCV infection or if testing is mandated by local health authority; if indicated to be collected, required analytes are shown in Table 6. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results.

8.6.6.3. Serum Tumor Markers

Serum tumor markers (CEA or CA-125) should be collected locally at Screening and Day 1 of every Cycle until treatment discontinuation; sample may be collected up to 72 hours prior to the scheduled time point. Type of tumor marker collected is dependent on cancer type, as follows:

Tumor Type	Tumor Marker
Colorectal Cancer	Carcinoembryonic Antigen (CEA)
Ovarian Cancer	Cancer Antigen 125 (CA-125)

8.6.7. Central Laboratory Assessments

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

8.7. Efficacy Assessments

8.7.1. RECIST v1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and

2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.7.2. iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST maybe used by the Investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 2. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy, then experience subsequent disease response. This data will be captured in the clinical database.

- **If participant is clinically stable, continue study intervention per protocol**
    - Continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired)
    - Continue investigator assessment per iRECIST
    - Record scan data (date, method, assessment) within eCRF
- **If the participant is not clinically stable, best medical practice is to be applied.**

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status
- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

8.7.3. Treatment Beyond Progression

A minority of participants treated with immunotherapy drugs may derive clinical benefit despite initial evidence of progressive disease per RECIST v1.1. Immunotherapy treatment-induced enhanced inflammation within the tumor could lead to increase in tumor size. Also, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With additional treatment the anti-tumor activity may dominate the inherent tumor growth kinetics and become clinically apparent. Hence, it is important to avoid premature discontinuation of the study drug. The decision to continue treatment beyond Investigator-assessed RECIST should be discussed with Sponsor Medical Monitor and documented in study records. Participants should meet the following criteria to be considered for treatment beyond progression by RECISTv1.1:

- Participant is having clinical benefit as assessed by Investigator
- There is no rapid disease progression
- The study drug is well tolerated
- Participant has stable performance status

- Treatment beyond progression will not delay an immediate intervention to prevent serious complications of disease progression, for example, in CNS metastases

Participants undergoing treatment beyond progression will continue radiographic assessments in accordance with the Schedule of Activities. If there is an additional 10% increase in tumor burden with a minimum of 5 mm increase from time of initial progression, study drug treatment will be permanently discontinued unless the clinical judgement of the investigator is that continuing treatment is in the participant's best interest.

Participants that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease and should be discontinued from study treatment.

8.7.4. Tumor Imaging and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

The same type of scan should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

CT scans are preferred over other tumor imaging methods. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same type of scan should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Notes:

1) *For the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.*
2) *In general, imaging should include the chest, abdomen, and pelvis.*
3) *For participants with head and neck cancer, imaging should also include the head and neck.*

At screening, participant eligibility will require radiographic documentation of at least one lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1 verified by investigator assessment prior to study treatment. All scheduled scans obtained throughout the trial for participants will be reviewed and recorded in the eCRF. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be recorded in the eCRF if it shows disease progression, or if it is used to support a response assessment.

8.7.5. Initial Imaging at Screening

Initial tumor scans must be performed within 30 days prior to the first dose of study treatment. 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 treatment.

The site study team must review screening scans to confirm that the participant has measurable disease per RECIST v1.1. Tumor lesions located in a previously irradiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. If a participant only has lesions in an area previously irradiated or subjected to locoregional therapy but has shown measurable progression subsequent to the therapy, then the participant will be allowed to enroll. Additionally, it is recommended that tumor lesions selected for biopsy **not** be selected as target lesions.

Note: If brain scans are performed to document the stability of existing metastases, the brain MRI should be acquired during screening. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.7.6. Tumor Imaging During the Study

The first imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the start of treatment. Subsequent tumor scans should be performed every 9 weeks (63 days ± 7 days) thereafter or more frequently if clinically indicated. After 1 year of treatment, scans may be performed according to standard of care schedule. **Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.** Scans should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue treatment beyond progression, see Section 8.7.2 and 8.7.3), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

If disease progression is confirmed, study intervention will be discontinued. Exceptions are detailed in Section 8.7.2 and Section 8.7.3.

8.7.7. End of Treatment and Follow-Up Tumor Imaging

If participants discontinue study treatment, tumor scans should be performed at the time of discontinuation (± 4 weeks) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study treatment due to documented disease progression, this is the final required tumor scan if the investigator elects not to implement iRECIST.

If participants discontinue study treatment without documented disease progression, every effort should be made to monitor disease status by acquiring tumor scans using the same schedule used while on treatment (every 9 weeks or per standard of care). Scans are to be continued until one of the following conditions are met:

- Disease progression as defined by RECIST 1.1*
- The start of a new anticancer treatment

- Pregnancy
- Death
- Withdrawal of consent
- The end of the study

*Participants who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed when clinically appropriate

8.8. Pharmacokinetic Assessments

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

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

8.9. Biomarker and Correlative Assessments

Tumor, ctDNA, Immunophenotyping, and serum cytokine samples will be collected at the visits outlined in the Schedule of Assessments. 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.

8.9.1. Tumor Biopsies

8.9.1.1. Tumor Tissue Collection Requirements

Tumor biopsy samples are required for participation in the study.

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

- **Screening (mandatory*):** A fresh biopsy or collection of archival tumor tissue (≤ 5 years) from a previous biopsy is required at Screening.
    - A baseline biopsy obtained for other purposes (i.e., not an NC410-02 procedure) may be utilized if the participant has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (Cycle 1 Day 1).
    - Fresh tumor biopsies should be taken from nontarget lesions when possible.

- **On-treatment (mandatory*):** An on-treatment biopsy (fresh) must be obtained anytime during Week 8 ± 3 days (prior to 1st on-treatment scan). **Note*:*** On-treatment biopsies should be performed at the same site as the screening biopsy whenever possible.
- **At the End of Treatment (optional):** A third optional tumor specimen referred to as the End of Treatment (EOT) biopsy may be obtained at the time that study treatment has been discontinued.

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

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

8.9.1.2. Tumor Tissue Assessment

Tumor biopsy samples will be used to investigate molecular signatures associated with response or resistance to treatment with the study treatment. DNA and/or RNA may be extracted from these samples to perform the following analyses, but are not limited to, 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.

8.9.2. Immunophenotyping Correlative Assessment

Immunophenotyping 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, but are not limited to, may be performed based upon emerging data.

8.9.3. Serum Pharmacodynamic Assessment

Serum samples will be evaluated to assess evidence of NC410 activity when combined with pembrolizumab.

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, chemokines, LAIR2, sLAIR-1, C1q, Collagen derived products [CDP]) pre- and on-treatment with NC410 when combined with pembrolizumab. Other assays relevant to the objectives of the study may be performed based on emerging data.

8.9.4. Serum and Immunophenotyping Assessments

Biomarkers will be analyzed in serum and Immunophenotyping samples collected at baseline and on the days and times as outlined in the Schedule of Assessments. 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.

9. SAFETY MONITORING AND REPORTING

9.1. Adverse Events (AEs)

9.1.1. Adverse Event Definition

For the purposes of this protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related, that occurs after a participant provides informed consent and through the follow-up period. Both nonserious and serious AEs (SAEs) will be monitored throughout the study. AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

9.1.2. Serious Adverse Event Definition

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 participant '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 participant 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.

9.1.3. Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor **within 24 hours of awareness** by the Investigator.

For the time period beginning when the consent form is signed until initiation of study treatment, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 24 hours to the Sponsor if it causes the participant to be excluded from the trial or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Events of clinical interest for this trial include:

1) An overdose of Pembrolizumab or NC410, as defined in Section 9.1.3.1– Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2) An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. *

   ***Note**: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

3) An adverse event meeting definition of a DLT as defined in Section 5.9.1.

9.1.3.1. Reporting of an Overdose

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. For NC410, a definitive “overdose” level is unknown at this time. For the purpose of this trial, an overdose of NC410 will be defined as a participant receiving a dose of NC410 in excess of that assigned to them at the time of study treatment, unless the alternative dose level was otherwise authorized by the Sponsor prior to administration.

Any overdose of a study participant with either NC410 or pembrolizumab with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor or its designee. If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

9.1.3.1.1. Treatment of Overdose (Pembrolizumab or NC410)

No specific information is available on the treatment of overdose of pembrolizumab or NC410. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.1.4. 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 study treatment exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on the nature of pembrolizumab and NC410, its mechanism of action, and reported experience with other immunotherapies. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Guidance for the assessment, diagnosis, and management of irAEs is provided in Section 5.8.2. Suspected irAEs should be discussed with the Sponsor.

9.1.5. Reporting of AEs

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

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

If an event is not classified by NCI CTCAE, the severity of the AE will be graded according to Table 8 to estimate the grade of severity.

Table 8: 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.
Grade 5	Death

The occurrence of AEs should be sought by nondirective questioning of the participant 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 participant during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (NCI CTCAE v5.0 Grade 1 to 5).

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (Section 9.1.7).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy (e.g. procedure), this action should be recorded on the AE eCRF and the event should be correlated as the indication on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy eCRFs as applicable.

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

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

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

- All AEs, SAEs and other reportable safety events (including ECIs) that occur after the consent form is signed but before first study treatment must be reported by the investigator *if they cause the participant to be excluded from the study or are the result of a protocol-specified intervention*, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure. SAEs and ECIs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier.
- All AEs or ECIs (Events of Clinical Interest) from the time of first study treatment through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria (SAEs) or ECIs, from the time of first study treatment through 90 days following cessation of study treatment, or 30 days following cessation of

study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of first study treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related (pembrolizumab and/or NC410).

9.1.7. Reporting of SAEs or ECIs

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

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

9.2. Laboratory Test Abnormalities

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

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

9.3. Emergency Unblinding of Treatment Assignment

Not applicable.

9.4. Pregnancy

If a participant inadvertently becomes pregnant while on study treatment with NC410 and pembrolizumab, the participant will be immediately discontinued study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

When a pregnancy has been confirmed in a participant (or a male participant's partner) during maternal or paternal exposure to study drug within 120 days of the last dose of study treatment the following procedures should be followed to ensure participant safety:

- The study drug must be discontinued immediately (female participants only).
- Consent must be obtained from female partners of male participants.
- 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 participants 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 participant, to determine whether it is in the participant's best interest to resume study drug and continue participation in the study.
- The EOT visit evaluations must be performed (female participants only).

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

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

9.5. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in the NC410 and Pembrolizumab IB. Additional safety information collected between IB updates will be communicated to Investigators as it becomes available. Any important new safety information should be discussed with the participant during the study, as necessary, and provided to the IRB. If new significant risks are identified, they will be added to the ICF.

9.6. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established for this open-label study. For Phase 1b, 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 DSMB 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 DSMB will be detailed in the DSMB Charter.

9.7. 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 pembrolizumab and NC410, its mechanism of action, and reported experience with other immunotherapies. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Guidance for the assessment, diagnosis, and management of irAEs is provided in Section 5.8.2. Suspected irAEs should be discussed with the medical monitor.

9.8. Reporting Product Complaints

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

NextCure contact information for reporting product complaints:

Email: NCClin@nextcure.com

Email participant line should include: "***NC410-02 Product Complaint***"

Mail: NextCure, Inc.
Attn: Clinical Operations
9000 Virginia Manor Road
Beltsville, MD 20705 USA

10. STATISTICS

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

Tabular summaries will be presented by dose groups. Categorical data will be summarized by the number and percentage of participants 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 participants who receive any dose of pembrolizumab and/or NC410. Additional details of statistical analyses will be described in the Statistical Analysis Plan (SAP).

10.1. Statistical Analysis Plan

Key elements of the statistical analysis plan are summarized in Table 9. The comprehensive plan is provided in Sections 10.2 through 10.6.

Table 9: Key Elements of the Statistical Analysis Plan

Element	Plan for analysis
Study Design Overview	A Phase 1b/2, Open-Label, Safety, Tolerability and Efficacy Study of NC410 Plus Pembrolizumab for Participants with Advanced Unresectable and/or Metastatic Immune Checkpoint Inhibitor (ICI) Refractory Solid Tumors or ICI Naïve MSS/MSI-Low Solid Tumors The study applies a modified TPI design for dose finding in Phase 1b. The study uses an optimal Simon 2-stage trial design in Phase 2 to rule out an unacceptably low response rate (CR+PR) in favor of an improved response rate.
Analysis Populations	Safety Analysis Set (SAS): The SAS will include all the participants who receive any amount of NC410 and/or pembrolizumab and will be used for summaries and analyses of safety data. PK Analysis Set (PAS): The PAS will include all the participants whose blood samples are collected for PK analysis and will be used for PK data summaries and analyses. Full Analysis Set (FAS): The FAS includes all participants enrolled in the study who received at least one full dose of pembrolizumab and one full dose of NC410. The FAS will be used for summaries and analyses of all data that are not safety or PK

Element	Plan for analysis
Primary Endpoint(s)	Phase 1B: • Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). Note: Toxicity grading per NCI CTCAE v5.0 • The recommended Phase 2 dose (RP2D) of NC410 when combined with standard dose Pembrolizumab will be defined in participants with advanced unresectable and/or metastatic ICI refractory solid tumors (regardless of MSI status) OR ICI naïve MSS/MSI-low solid tumors Phase 2: • Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: o Objective Response Rate (ORR) based on RECIST v1.1 as assessed by the investigator
Secondary Endpoints	Phase 1B: • Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: o Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR) and Progression-free Survival (PFS), based on RECIST v1.1 as assessed by the investigator o Overall Survival (OS) • Assessment of PK of NC410 concentration in serum, as well as assessment of combination treatment on the PK/PD profile Phase 2: • Assessment of antitumor activity will be used to evaluate the clinical benefit of NC410 in combination with Pembrolizumab, including: o Duration of Response (DoR), Disease Control Rate (DCR) and Progression-free Survival (PFS) based on RECIST v1.1 as assessed by the investigator o Overall Survival (OS) • Assessment of PK of NC410 concentration in serum, as well as assessment of combination treatment on the PK/PD profile • Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs). **Note:** Toxicity grading per NCI CTCAE v5.0
Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	Using the FAS, all the efficacy data will be summarized by phase, dose group, and cohort. The PK analyses will be based off the PAS, and PK time-concentration data will be summarized, listed, and plotted. PK parameters (AUC_{0-336}, $AUC_{0-\infty}$, Cmax, $t_{½}$, etc.) derived from time-concentration data will be summarized
Treatment Assignment	This is an open-label study.

Element	Plan for analysis
Statistical Methods for Safety Analyses	The safety assessments include adverse events, laboratory tests and vital signs. All the safety data in the SAS will be summarized and listed by phase, treatment group, and cohort.
Interim Analyses	No formal interim analysis is planned. However, the safety, PK and efficacy data will be regularly reviewed and monitored for decisions involving dose escalation in Phase 1b and continuation in Phase 2 of the study.
Multiplicity	Individual cohorts will be evaluated independently.
Sample Size and Power	The overall study sample size is approximately 131. Phase 1b: The planned sample size is up to 102 participants. Phase 2: The planned sample size is up to 107 participants, across multiple tumor types. The Simon 2-stage trial design provides 90% power to reject the null hypothesis within each cohort.

Abbreviations: AE = adverse event; AUC = area under the curve; C_{max} = maximum concentration of drug; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; ICI = immune checkpoint inhibitor; MSI = microsatellite instable; MSS = microsatellite stable; NCI = National Cancer Institute; ORR = objective response rate; PAS = Pharmacokinetics Analysis Set; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAS = Safety Analysis Set; $t_{1/2}$ = half-life; TPI = toxicity probability interval.

10.2. Study Populations

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

10.3. Selection of Sample Size

Approximately 209 eligible participants in Phase 1b and Phase 2 (102 + 107) will be included in this study.

10.3.1. Sample Size for Phase 1

The primary objective of the dose escalation in Phase 1b of the study is to determine the MTD or RP2D of NC410 in combination with a fixed dose of pembrolizumab. A modified Toxicity Probability Interval (mTPI) (Ji, 2013) with a target dose limiting toxicity (DLT) rate of approximately 30% will be applied for dose escalation and confirmation to determine a recommended Phase 2 dose (RP2D) for NC410 in combination with Pembrolizumab. The sample size is not fixed and will vary based on emerging safety data at the doses studied for the Phase 1b.

10.3.2. Sample Size for Phase 2

Phase 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of NC410 in combination with pembrolizumab. The sample size for each tumor type will be guided by the Simon 2-stage design (Simon, 1989).

For participants with ICI refractory solid tumors (regardless of MSI status), published data with ICI monotherapy suggests response rates of approximately 5-10% have been obtained (Kitagawa, 2020; Yang, 2020). Thus, the objective for ICI- refractory cohort participants will be to improve upon this estimated 5-10% response rate. The trial will be conducted in the ICI refractory solid tumor cohort (CRC, Gastric including GE junction, Esophageal, H&N, Lung, Cervical and Ovarian cancers) using an optimal Simon two-stage Phase 2 trial design to rule out an unacceptably low response rate (CR+PR) of 10% (p0=0.10) in favor of an improved response rate of 30% (p1=0.30) in order to determine if there is a greater response to the combination of NC410 and Pembrolizumab in these participants. The null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. In the first stage, 12 evaluable participants will be accrued. If there are 1 or fewer responses in these 12 participants, enrollment in this arm will be stopped. If 2 or more of the first 12 participants have a response, then accrual would continue until a total of 35 evaluable participants have been treated in that arm. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. The null hypothesis will be rejected, further investigation of the drug is warranted, if 6 or more responses are observed in 35 participants. This design yields a type I error rate of .0977 and power of .9014 when the true response rate is 0.3.

For participants with ICI naïve and MSS or MSI low solid tumors **(**CRC, Gastric including GE junction, Ovarian), published data suggests response rates of approximately 0-10% with ICI have been obtained (Marmorino, 2020; Yang, 2020). Thus, the objective for this ICI- naïve participant will be to improve upon this estimated 0-10% response rate. The trial will be conducted in each disease cohort (CRC, Gastric including GE junction, and Ovarian) using an optimal Simon two-stage phase 2 trial design to rule out an unacceptably low response rate (CR+PR) of 5% (p0=0.05) in favor of an improved response rate of 25% (p1=0.25) in order to determine if there is a greater response to the combination of NC410 and Pembrolizumab in these participants (Study schema below). The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. In the first stage, 9 evaluable participants will be accrued. If there are 0 responses in these 9 participants, enrollment in corresponding arm will be stopped. If 1 or more of the first 9 participants have a response, then accrual would continue until a total of 24 evaluable participants have been treated each disease cohort in that arm. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. The null hypothesis will be rejected, further investigation of the drug is warranted, if 3 or more responses are observed in 24 participants. This design yields a type I error rate of .0931 and power of .9028 when the true response rate is 0.25.

10.3.3. Level of Significance

The optimal Simon 2-stage trial designs used in Phase 2 have a one-sided level of significance of 0.0977 and 0.0931. No other hypothesis tests are planned for this study. Ninety-five percent

confidence intervals may be calculated and presented for summary purposes, which is based on a significance level of 0.05.

10.4. 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 1b and continuation in Phase 2 of the study.

10.5. Statistical Analyses

10.5.1. Safety Analyses

The safety assessments include adverse events, laboratory tests, and vital signs. All the safety data in the SAS will be summarized and listed by phase, treatment group, and cohort.

10.5.1.1. 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 5.

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

10.5.2. Summary of Baseline Characteristics, Demographics and Other Analyses

The number and percentage of participants screened, treated, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, cancer history and diagnosis, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

10.5.3. PK Analyses

The PK analyses will be based off the PAS, and PK time-concentration data will be summarized, listed, and plotted. PK parameters ($AUC_{0\text{-}336}$, $AUC_{0\text{-}\infty}$, C_{max}, $t_{½}$, etc.) derived from time-concentration data will be summarized.

10.5.4. Efficacy Analyses

The response will be assessed by CT/MRI image during screening and every 9 weeks (63 ± 7 days) post-dosing for 1 year and then per standard of care. The efficacy study endpoints include ORR, DCR, DoR, PFS, and OS. Tumor response will be determined according to RECIST v1.1. Time-to-event data (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. All the efficacy data will be summarized by phase, dose group, and cohort.

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

  OS = (Death or LKA date) – (date of first dose of study drug + 1)

10.5.5. Pharmacodynamic and Biomarkers Analysis

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

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

- Correlation analysis between PD biomarkers and the disease response to treatment with NC410 when combined with pembrolizumab.

The immunogenic potential of NC410 will be assessed by summarizing the number and percentage of participants 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.

10.6. Analyses for Data Safety Monitoring Board

There will be no formal analysis for data safety monitoring board review.

11. STUDY AND DATA MANAGEMENT

11.1. Training of Study Site Personnel

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

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

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

11.2. Monitoring of the Study

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the NC410-02 Laboratory Manuals and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating participants. This will require direct access to all original records for each participant (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the participant's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the participant.

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

11.2.1. Source Data

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

The primary source document for this study will be the participant'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 participant. A study monitor representing the sponsor will review the source documents against the eCRF on a regular basis throughout the study.

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

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

11.2.2. Archiving of Study Documents

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

11.3. Study Timetable and End of Study

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

11.4. Data Management

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

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

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

11.5. Medical Monitor Coverage

Each participant will be provided with contact information for the PI and the site coordinator(s). In an emergent situation, a participant 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 participant should provide contact information for the site coordinator(s) or the PI.

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

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1. Ethical Conduct of the Study

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

12.2. Participant 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 participants must be maintained. Participants will be identified by their initials and an assigned participant number on eCRFs and other documents submitted to the sponsor. Documents that identify the participant beyond initials and participant 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 participants, 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 participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, a NextCure medical monitor or an investigator might know a participant's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

12.3. 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 participants.

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

The IRB/IEC should approve all advertising used to recruit participants 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 participant 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.

IRB/IECs must be informed of:

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

12.4. Informed Consent

A copy of the proposed ICF must be submitted to the sponsor for review and comment prior to submission to the reviewing IRB/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 participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each participant is notified that they are free to discontinue from the study at any time
- Ensure that each participant is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each participant 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 participant
- Ensure that any incentives for participants who participate in the study as well as any provisions for participants harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

12.5. Changes to the Protocol and Informed Consent Form

Protocol revisions will be prepared and approved by NextCure and the medical monitor. Minor revisions will be submitted as administrative changes. If there are any substantial changes to the

study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

All protocol amendments will be signed by the PI and approved by the relevant IRB/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 12.3.

If a protocol amendment alters the study design, increases potential risk to the participant 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 participants prior to enrollment and must be used to obtain informed consent from participants 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.

12.6. 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.

13. REFERENCES

Afshar-Kharghan V. The role of the complement system in cancer. J Clin Invest. 2017;127:780-9.

Blank C, Brown I, Peterson AC, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 2004;64:1140-5.

Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol. 2004;173:945-54.

Chiou VL, Burotto M. Pseudoprogression and Immune-Related Response in Solid Tumors. J Clin Oncol. 2015;33:3541-3.

Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A. 2010;107:4275-80.

Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28:4531-8.

Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol. 2005;23:2346-57.

Flies DB, Higuchi T, Harris JC, Jha V, Gimotty PA, Adams SF. Immune checkpoint blockade reveals the stimulatory capacity of tumor-associated CD103(+) dendritic cells in late-stage ovarian cancer. Oncoimmunology. 2016;5:e1185583.

Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219-42.

Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2005;23:515-48.

Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65:1089-96.

Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med. 2008;358:2698-703.

Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol. 2013;31:1785-91.

Kitagawa S, Hakozaki T, Kitadai R, Hosomi Y. Switching administration of anti-PD-1 and anti-PD-L1 antibodies as immune checkpoint inhibitor rechallenge in individuals with advanced non-small cell lung cancer: Case series and literature review. Thorac Cancer. 2020;11:1927-33.

Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020;131:68-75.

Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;372:2509-20.

Lebbink RJ, Raynal N, de Ruiter T, Bihan DG, Farndale RW, Meyaard L. Identification of multiple potent binding sites for human leukocyte associated Ig-like receptor LAIR on collagens II and III. Matrix Biol. 2009;28:202-10.

Lebbink RJ, van den Berg MC, de Ruiter T, et al. The soluble leukocyte-associated Ig-like receptor (LAIR)-2 antagonizes the collagen/LAIR-1 inhibitory immune interaction. J Immunol. 2008;180:1662-9.

Marmorino F, Boccaccino A, Germani MM, Falcone A, Cremolini C. Immune Checkpoint Inhibitors in pMMR Metastatic Colorectal Cancer: A Tough Challenge. Cancers (Basel). 2020;12:2317.

Meyaard L. The inhibitory collagen receptor LAIR-1 (CD305). J Leukoc Biol. 2008;83:799-803.

Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13:2151-7.

Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A. 2001;98:13866-71.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Olde Nordkamp MJ, van Eijk M, Urbanus RT, Bont L, Haagsman HP, Meyaard L. Leukocyte-associated Ig-like receptor-1 is a novel inhibitory receptor for surfactant protein D. J Leukoc Biol. 2014;96:105-11.

Olde Nordkamp MJ, van Roon JA, Douwes M, de Ruiter T, Urbanus RT, Meyaard L. Enhanced secretion of leukocyte-associated immunoglobulin-like receptor 2 (LAIR-2) and soluble LAIR-1 in rheumatoid arthritis: LAIR-2 is a more efficient antagonist of the LAIR-1-collagen inhibitory interaction than is soluble LAIR-1. Arthritis Rheum. 2011;63:3749-57.

Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol. 2005;25:9543-53.

Pearce OMT, Delaine-Smith RM, Maniati E, et al. Deconstruction of a Metastatic Tumor Microenvironment Reveals a Common Matrix Response in Human Cancers. Cancer Discov. 2018;8:304-19.

Peng DH, Rodriguez BL, Diao L, et al. Collagen promotes anti-PD-1/PD-L1 resistance in cancer through LAIR1-dependent CD8(+) T cell exhaustion. Nat Commun. 2020;11:4520.

Pilon-Thomas S, Mackay A, Vohra N, Mule JJ. Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol. 2010;184:3442-9.

Ramos MIP, Tian L, de Ruiter EJ, et al. Cancer immunotherapy by NC410, a LAIR-2 Fc protein blocking human LAIR-collagen interaction. Elife. 2021;10:e62927.

Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009;229:114-25.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and

Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47:373-80.

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:e143-e52.

Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1-10.

Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer. 2014;2:3.

Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 2003;63:6501-5.

Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. Semin Oncol. 2010;37:430-9.

Yang K, Li J, Sun Z, Zhao L, Bai C. Retreatment with immune checkpoint inhibitors in solid tumors: a systematic review. Ther Adv Med Oncol. 2020;12:1758835920975353.

Zhang L, Gajewski TF, Kline J. PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model. Blood. 2009;114:1545-52.

Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20:337-47.

APPENDIX 1. SIGNATURES

Sponsor Signature(s)

A Phase 1b/2, open-label, safety, tolerability, and efficacy study of NC410 plus Pembrolizumab for participants with advanced unresectable and/or metastatic immune checkpoint inhibitor (ICI) refractory solid tumors or ICI naïve MSS/MSI-low solid tumors.

I agree to the terms of this protocol.

DocuSigned by:
Han Myint
Signer Name: Han Myint
Signing Reason: I approve this document
Signing Time: 30-Jul-2024 | 07:39 EDT
DE96C6818FF1451F831BD4A4382A0B80

_____

Signature and date

Han Myint, MD
Chief Medical Officer
NextCure, Inc.
9000 Virginia Manor Road, Suite 200,
Beltsville, MD 20705 USA
Telephone number: 240-399-4900

Sponsor Signature(s)

A Phase 1b/2, open-label, safety, tolerability, and efficacy study of NC410 plus Pembrolizumab for participants with advanced unresectable and/or metastatic immune checkpoint inhibitor (ICI) refractory solid tumors or ICI naïve MSS/MSI-low solid tumors.

I agree to the terms of this protocol.

DocuSigned by:
Ashley Martz
Signer Name: Ashley Martz
Signing Reason: I approve this document
Signing Time: 29-Jul-2024 | 15:10 EDT
4BA2E4D443C64B87ABE9A66CD81EA674

_____

Signature and date

Ashley Martz
Associate Director, Clinical Operations
NextCure, Inc.
9000 Virginia Manor Road, Suite 200, Beltsville, MD 20705 USA
Telephone number: 859-468-8632

Signature of Principal Investigator

A PHASE 1B/2, OPEN-LABEL, SAFETY, TOLERABILITY AND EFFICACY STUDY OF NC410 PLUS PEMBROLIZUMAB FOR PARTICIPANTS WITH ADVANCED UNRESECTABLE AND/OR METASTATIC IMMUNE CHECKPOINT INHIBITOR (ICI) REFRACTORY SOLID TUMORS OR ICI NAÏVE MSS/MSI-LOW 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 participants 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. DESCRIPTION OF THE IRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and to guide decisions about changes in management.

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show radiological progressive disease by RECIST 1.1, the Investigator will decide whether to continue a participant on study treatment until repeat scans are obtained, as described in Section 8.7.2.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: The iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression. At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Scans

On the confirmatory scans, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered progressive disease by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial progressive disease threshold (by RECIST 1.1)

Additional scans for confirmation are to be scheduled 4 to 8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial progressive disease threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve. In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Scan

If repeat scans do not confirm progressive disease per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study intervention is to continue and the regular

scan schedule is to be followed. If progressive disease is confirmed, participants may be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful study intervention may be continued after consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.7.6.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie., after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the progressive disease threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudoprogression.
    - Non-target lesions
- If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory scan above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial progressive disease, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until new or worsening causes of progression indicates iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour, 2017).

APPENDIX 3. 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 5 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 participant.
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 participant.
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 participant to perform activities of daily living (eating, ambulation, toileting, etc.).
Grade 5 (death)	An event that resulted in death.

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 9.1.5. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

The NCI CTCAE v5.0 can be downloaded from the Cancer Treatment Evaluation Program (CTEP) (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

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 participant '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 participant 's medical record).

APPENDIX 4. 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, 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 participant (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 participant (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 5. 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

From: Oken, 1982.

APPENDIX 6. SUMMARY OF CHANGES

Table 10: Summary of Protocol Changes

Protocol Version	Date
Version 1.0 (Original)	28APR2022
Amendment 1 Version 2.0	30SEP2022