Protocol Number: NIT-110

Official Title: An Open-label Phase 1b/2a Study of NT-I7 (Efineptakin Alfa) in Combination With Pembrolizumab in Subjects With Relapsed/Refractory Advanced Solid Tumors

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Statistical Analysis Plan

An Open-label Phase 1b/2a Study of NT-I7 (efineptakin alfa) in Combination with Pembrolizumab in Subjects with Relapsed/Refractory Advanced Solid Tumors

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Study Drug:	NT-I7
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History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	4 Jan2023	Original document (based on Protocol V5.0 dated on 17MAR2022)
2.0	01May2025	Updated based on Protocol V7.0 dated on 26Oct2023 and the comments from NIT

Statistical Analysis Plan Review and Approval

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Date

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Date

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Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Concentration Time-Curve
BOR	Best Overall Response
BQL	Below the Quantifiable Limit
BUN	Blood Urea Nitrogen
CXDY	Cycle X Day Y
CI	Confidence Interval
C_{max}	Maximum Serum Concentration
C_{min}	Minimum Serum Concentration
CPI	Checkpoint Inhibitor
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organization
CL/F	Apparent Clearance after Extra-Vascular Dose
cCSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCR	Disease Control Rate
DL	Dose Level
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
IF	Immunofluorescence
IM	Intramuscular
iCPD	Immune-Confirmed Progressive disease
iCR	Immune-Complete Response
iPR	Immune-Partial Response
iRECIST	Immune-Response Evaluation Criteria in Solid Tumors
IRR	Infusion-related Reaction
iNE	Immune-Not Evaluable
INR	International Normalized Ratio

iSD	Immune-Stable Disease
ISR	Injection Site Reaction
iUPD	Immune-Unconfirmed Progressive Disease
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MED	Maximum Effective Dose
MTD	Maximum Tolerated Dose
MSS-CRC	Microsatellite Stable Colorectal Cancer
NCI	National Cancer Institute
NE	Not Evaluable
NIT	NeoImmuneTech, Inc.
NSCLC	Non-Small Cell Lung Cancer
OC	Ovarian Cancer
ORR	Objective Response Rate
OS	Overall Survival
PC	Pancreatic Cancer
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic/Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
Q3W	Once Every 3 Weeks
Q6W	Once Every 6 Weeks
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
R/R	Relapsed/Refractory
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvic Transaminase
SOC	System Organ Class
STD	Standard Deviation
$T_{1/2}$	Terminal Elimination Phase half-life
TBL	Total Bilirubin
TCR	T Cell Receptor
TEAE	Treatment-Emergent Adverse Event
TIL	Tumor Infiltrating Lymphocyte
TME	Tumor Microenvironment
T_{max}	Time to Maximum Serum Concentration

TNBC	Triple Negative Breast Cancer
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
Vz/F	Apparent Volume of Distribution

1. INTRODUCTION

This document is the Statistical Analysis Plan (SAP) for study "An Open-label Phase 1b/2a Study of NT-I7 (efineptakin alfa) in Combination with Pembrolizumab in Subjects with Relapsed/Refractory Advanced Solid Tumors". It is prepared based on Protocol V7.0 dated on 26Oct2023.

Populations for analysis, data handling rules, and statistical methods are described within this document. The statistical analysis and summary tabulations described in this document, including safety, efficacy, and pharmacokinetics (PK), will provide the basis for the results sections of the clinical study report (CSR) for this trial.

In addition, same statistical methods and procedure described in SAP will be followed to report results for interim related analysis.

The statistical analysis for the study will be performed by NJS Associates, a NeoImmuneTech, Inc. (NIT) designated clinical research organization.

1.1 Objectives

This is a multicenter, open-label Phase 1b/2a study to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), and to assess the safety, and tolerability of NT-I7 in combination with pembrolizumab in subjects with checkpoint inhibitor (CPI) treated relapsed/refractory (R/R) tumors (Triple Negative Breast Cancer [TNBC], Non-Small Cell Lung Cancer [NSCLC], Small Cell Lung Cancer [SCLC]), and CPI naïve R/R tumors (Microsatellite Stable Colorectal Cancer [MSS-CRC], Pancreatic Cancer [PC], and Ovarian Cancer [OC]).

1.1.1 Primary Objectives

Phase 1b:

- To determine the safety and tolerability, including determination of the MTD and/or the RP2D of NT-I7 in combination with pembrolizumab in subjects with advanced solid tumors.

Phase 2a:

- To assess the preliminary anti-tumor activity of NT-I7 in combination with pembrolizumab in subjects with CPI treated R/R tumors (TNBC, NSCLC, SCLC), and CPI naïve R/R tumors (MSS-CRC, and PC), based on objective response rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immune Response Evaluation Criteria in Solid Tumors (iRECIST).

Biomarker Cohort:

- To assess a potential correlation between tumor infiltrating lymphocytes (TILs) and clinical benefits in subjects with CPI-naïve R/R OC.

1.1.2 Secondary Objectives

Phase 1b/2a/Biomarker Cohort:

- To make further assessment of the anti-tumor activity of NT-I7 in combination with pembrolizumab in these patient populations based on ORR (for Biomarker Cohort

only), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) by RECIST 1.1 and iRECIST.
- To evaluate immunogenicity of NT-I7 administered in combination with pembrolizumab in these patient populations.

Biomarker Cohort:
- To assess the safety and tolerability of NT-I7 in combination with pembrolizumab in subjects with CPI-naïve R/R OC.

1.1.3 Exploratory Objectives

Phase 1b/2a/Biomarker Cohort:
- To make a preliminary assessment of PK parameters in subjects enrolled in Phase 1b, Phase 2a, and Biomarker Cohort.
- To make a preliminary assessment of biomarkers that might act as pharmacodynamic indicators of NT-I7 activity in combination with pembrolizumab in subjects with CPI treated R/R tumors (TNBC, NSCLC, SCLC), and CPI naïve R/R tumors (MSS-CRC, PC, and OC).
- To make a preliminary assessment of biomarkers that might act as predictors of anti-tumor activity of NT-I7 in combination with pembrolizumab in subjects with CPI treated R/R tumors (TNBC, NSCLC, SCLC), and CPI naïve R/R tumors (MSS-CRC, and PC).

1.2 Endpoints

1.2.1 Primary Endpoints

Phase 1b:
- Incidence, nature, and severity of adverse events (AEs) graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.
- Incidence and nature of dose limiting toxicities (DLTs).
- Potential correlation of dose levels (DLs) with safety and efficacy parameters.

Phase 2a:
- ORR for each individual arm, defined as the percentage of subjects who have at least one confirmed partial response (PR) or complete response (CR), per RECIST 1.1 and iRECIST as determined by the investigator.

Biomarker Cohort:
- Number, distribution, and phenotype of TILs. CD8+TILs in tumor biopsy samples will be identified using a validated immunohistochemistry (IHC) assay and properly certified by a pathologist.

1.2.2 Secondary Endpoints

Phase 1b/2a/Biomarker Cohort:
- ORR (Biomarker Cohort only) defined as the percentage of subjects who have at least one confirmed PR or CR, per by RECIST 1.1 and iRECIST as determined by the investigator.

- DoR for the responders in each individual arm, defined as the time from the first occurrence of a documented objective response to the time of the first documented disease progression or death from any cause, whichever occurs first, per RECIST 1.1 and iRECIST as determined by the investigator.
- DCR for each individual arm, defined as proportion of subjects with a best overall response (BOR) of CR, PR or SD, per RECIST 1.1 and iRECIST as determined by the investigator.
- PFS for each individual arm, defined as the time from the first study treatment (Cycle 1, Day 1) to the first occurrence of disease progression or death from any cause, whichever occurs first, per RECIST 1.1 and iRECIST as determined by the investigator.
- OS for each individual arm, defined as the time from first study treatment (Cycle 1, Day 1) to death from any cause.
- Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to the prevalence of ADA at baseline.

Biomarker Cohort:

- Incidence, nature, and severity of AEs graded according to NCI CTCAE v5.0.

1.2.3 Exploratory Endpoints

Phase 1b/2a/Biomarker Cohort:

- Serum concentration of NT-I7 administered in combination with pembrolizumab at specified timepoints for the following parameters: area under the concentration time-curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and clearance (CL).
- Number, distribution, and phenotype of TILs (Biomarker Cohort to follow primary objective).
- PD-L1 expression.
- Expression of interferon γ (IFN-γ) and associated inflammatory gene expression in the tumor microenvironment (TME).
- Changes in TME that correlate with response or provide information on potential actionable causes for lack of clinical benefit. Exploratory analysis in pre- and on-treatment tumor biopsy samples from the same organ will be performed and compared between responders vs. non-responders to help elucidating the TME changes that may be correlated with response to treatment. Analysis may include, but not limited to, gene expression profiling and RNAseq, T cell receptor (TCR) repertoire diversity analysis by TCRseq, and immunostaining techniques such as multi-spectral immunofluorescence (IF).
- Changes in peripheral blood biomarkers, including but not limited to immunophenotyping and inflammatory mediators, will be analyzed in association with 1) the incidence of AEs and 2) as surrogated markers of response, TME changes and TIL infiltration.

1.3 Study Design

1.3.1 Overall Design

This is a multicenter, open-label Phase 1b/2a study of NT-I7 in combination with pembrolizumab. The study will include a dose escalation phase (Phase 1b) followed by a dose expansion phase (Phase 2a) and a Biomarker cohort (See study design in Figure 1).

The Phase 1b is designed to assess the safety and tolerability, including determination of the MTD and/or the RP2D, of NT-I7 in combination with pembrolizumab in subjects with advanced solid tumors. The Phase 1b will follow the standard 3+3 study design. Three DLs of NT-I7 are planned [DL 1 (480 μg/kg IM Q6W), DL 2 (960 μg/kg IM Q6W), and DL 3 (1200 μg/kg IM Q6W)], and up to 18 subjects will be enrolled (up to 6 subjects per DL). Doses may be de-escalated to one or two levels (e.g., 360 or 240 μg/kg IM Q6W) depending on the pre-defined DLT criteria. Pembrolizumab dose is fixed at 200 mg IV Q3W for all DLs. Upon completion of Phase 1b, the MTD was not reached. There was 1 DLT (Grade 3 ALT increased) observed at the highest DL tested (1,200 μg/kg; n=6 patients). The RP2D was determined to be NT-I7 1,200 μg/kg (IM Q6W) and pembrolizumab 200 mg (IV Q3W).

For Phase 2a, selected arms I, II, III, IV, and V will follow the Simon's minimax two-stage design which include the following indications: CPI treated R/R tumors (TNBC, NSCLC, SCLC), and CPI naïve R/R tumors (MSS-CRC and PC). Each arm will enroll up to 17 evaluable subjects in Stage 1 and, if the Go/No Go criterion is met, an additional 8 evaluable subjects will be enrolled in Stage 2 for a total of 25 evaluable subjects per arm. Exact 95% binomial Clopper-Pearson confidence interval (CI) estimates of ORR from each arm is planned to support the primary hypothesis tests. Study enrollment will continue while the first 17 subjects are undergoing evaluation to confirm response. Enrolment of up to 30 subjects per arm is planned to account for non-evaluable subjects and dropouts. Approximately 210 subjects are planned in total for the Phase 2a. Subjects in the Phase 2a will be treated at the RP2D for the combination as determined in the Phase 1b.

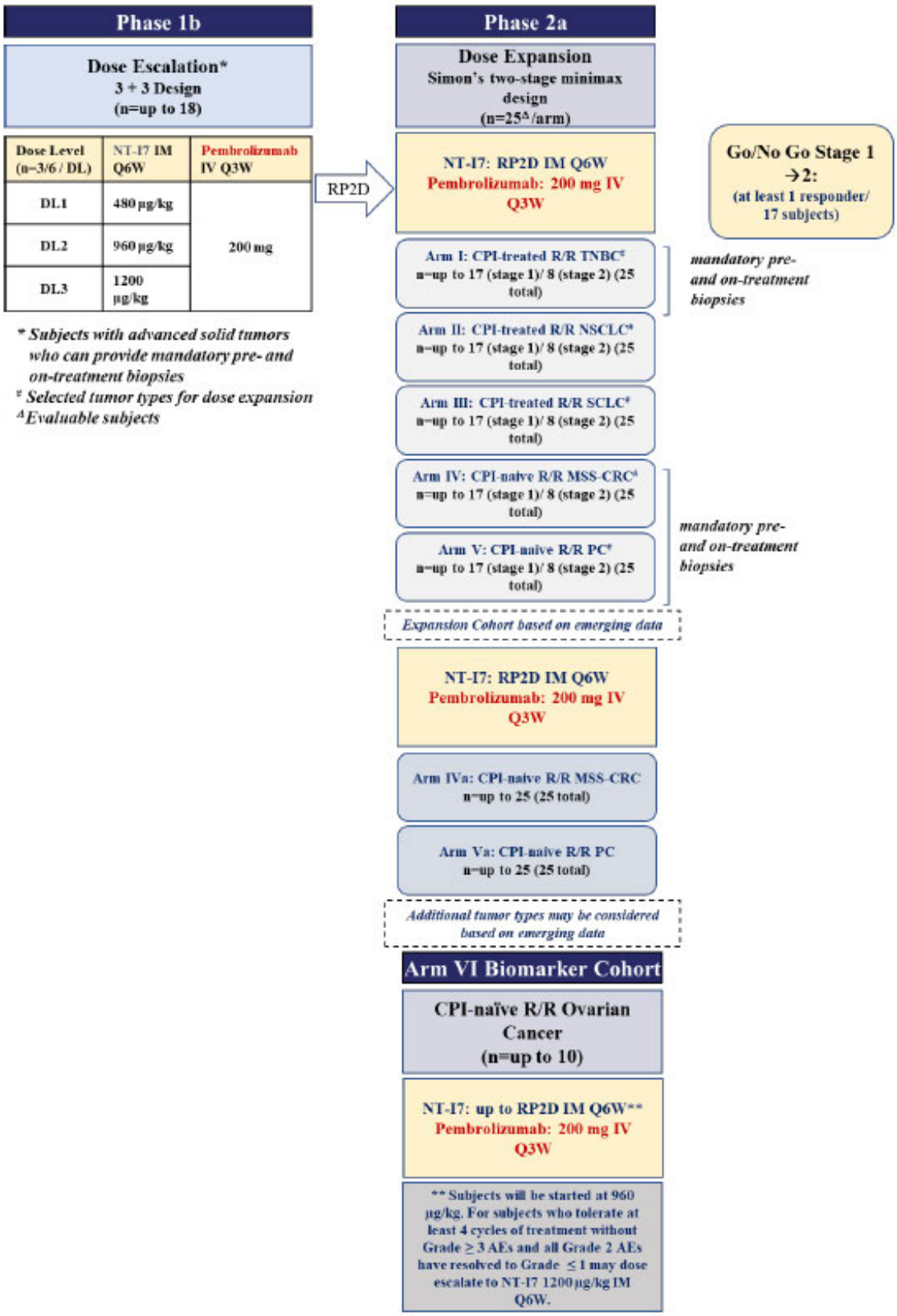
Arms IVa, Va, and the Biomarker Cohort will not follow the Simon's minimax two-stage design.

The Biomarker Cohort will enroll up to 10 evaluable subjects with CPI naïve R/R OC. The starting dose level of NT-I7 is planned at 960 μg/kg IM Q6W to further evaluate the tolerability of the starting regimen. Pembrolizumab dose is fixed at 200 mg IV Q3W. Subjects who tolerate at least 4 cycles of treatment without Grade ≥ 3 AEs and all Grade 2 AEs have resolved to Grade ≤ 1, the dose may be escalated to NT-I7 1200 μg/kg IM Q6W at Cycle 5. This cohort will test intra-patient dose escalation and collect samples for biomarker analyses at 2 different dosages.

One treatment cycle is defined as 21 days (3 weeks) with NT-I7 administered intramuscularly (IM) once every 6 weeks (Q6W), and pembrolizumab administered intravenously (IV) once every 3 weeks (Q3W).

On days where both drugs are given, pembrolizumab will be given prior to NT-I7. Treatment completion is defined as completion of 35 cycles of administration (approximately 2 years) with pembrolizumab and NT-I7.

Figure 1 Study Design



1.3.2 Dose Escalation (Phase 1b)

The starting dose of NT-I7 will be 480 μg/kg.

The 3 + 3 design will be conducted as follows. Initially, 3 subjects will be enrolled to a dose level; the occurrence of a single drug related DLT in one of these 3 subjects will prompt enrollment of up to 3 additional subjects to that same DL. When more than 1 DLT occurs in ≤ 6 subjects in a DL, dose escalation will be stopped, and this DL will be identified as the non-tolerated dose. Doses between the non-tolerated dose and the preceding lower dose, where ≤ 1 DLT occurred, may be explored to more precisely define the MTD.

The DLT is defined in Protocol Section 6.2. The DLT evaluation period is the first 21 days (3 weeks) of study treatment (Cycle 1, Day 1 to Day 21).

The dose escalation decisions will be communicated to all study sites by regularly scheduled teleconferences and follow up email correspondence documenting the decision and rationale.

The RP2D will be selected according to the following logic, taking into account the MTD determination from the dose escalation phase (Phase 1b) and the maximum effective dose (MED) level which is defined as the DL at which maximum effects on peripheral blood T-cell levels and intratumor T-cell levels are observed. The intratumor T-cell levels will dominate if the peripheral blood and intratumor T-cell levels differ. The available data will be assessed by the Data Monitoring Committee (DMC), which will include the protocol PI, study medical monitor, study statistician, and NeoImmuneTech's (NIT) designee to select the RP2D.

- If the MTD is determined AND
  - MTD = MED, then the RP2D = MTD = MED
  - MTD > MED, then the RP2D = MED
- If the MTD is not reached, then the RP2D = MED

Once the RP2D has been selected, the study will proceed to the dose expansion phase (Phase 2a) to further evaluate RP2D in a larger number of subjects and selected tumor types.

1.3.3 Dose Expansion (Phase 2a)

Subjects enrolled into the study during the dose expansion phase (Phase 2a) will be treated at the RP2D, which was determined to be 1200 μg/kg IM Q6W. Certain indications may be selected to expand in the expansion phase based on the emerging data.

For Phase 2a, Arms I, II, III, IV, and V will follow the Simon's two-stage minimax design. Arms IVa, Va, and the Biomarker Cohort OC will not follow the Simon's two-stage minimax design.

- Arm I: CPI treated R/R TNBC
- Arm II: CPI treated R/R NSCLC
- Arm III: CPI treated R/R SCLC
- Arm IV: CPI naïve R/R MSS-CRC
- Arm IVa: CPI naïve R/R MSS-CRC

- Arm V: CPI naïve R/R PC
- Arm Va: CPI naïve R/R PC
- Biomarker Cohort: CPI naïve R/R OC

In Stage 1, up to 17 evaluable subjects per arm will be enrolled and treated. If at least one subject achieves objective response (immune-complete response [iCR] or immune-partial response [iPR]) per iRECIST in an arm, that arm may be expanded by enrolling up to 8 evaluable additional subjects in Stage 2. Study enrolment will continue while the first 17 subjects are undergoing evaluation to confirm response. If no objective response is observed in an arm during Stage 1, further enrolment will be stopped in that arm.

1.3.4 Subject Expansion (Arm IVa and Va)

The Subject Expansion Cohort is designed to further assess the clinical benefits of NT-I7 in combination with pembrolizumab in subjects enrolled in the 2 selected cohorts based on emerging data. Subjects will receive Pembrolizumab at 200 mg IV Q3W and NT-I7 1200 μg/kg IM Q6W.

1.3.5 Biomarker Cohort

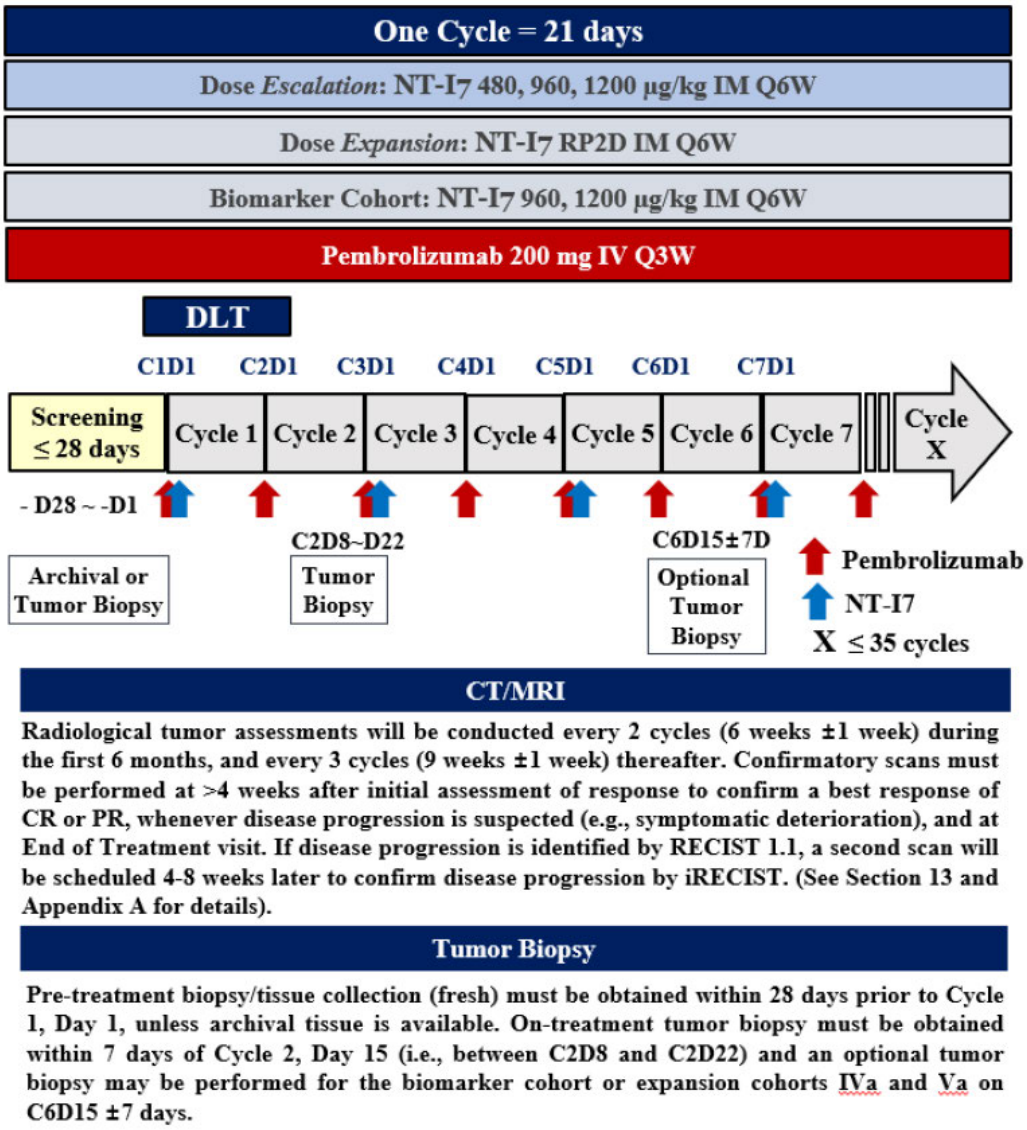
The Biomarker Cohort is designed to assess the correlation between TILs and clinical benefits of NT-I7 in combination with pembrolizumab in subjects with CPI naïve R/R OC. Up to 10 evaluable subjects will be enrolled in this cohort. The starting dose of NT-I7 will be 960 μg/kg IM Q6W. Pembrolizumab dose is fixed at 200 mg IV Q3W.

Subjects who tolerate at least 4 cycles of treatment without Grade ≥ 3 AEs and all Grade 2 AEs have resolved to Grade ≤ 1 may be dose escalated to NT-I7 1200 μg/kg IM Q6W.

1.3.6 Schedule of Procedures and Assessments

The schedule of procedures and assessments is descripted in protocol section 7. See Figure 2 for the treatment schema.

Figure 2 Treatment Schema



1.4 Sample Size Calculation

The Phase 1b will follow the standard 3+3 study design. Three DLs of NT-I7 are planned [DL 1 (480 µg/kg IM Q6W), DL 2 (960 µg/kg IM Q6W), and DL 3 (1200 µg/kg IM Q6W)], and up to 18 subjects will be enrolled.

ORR assessed by RECIST 1.1 and iRECIST will be considered as primary efficacy endpoints in each Phase 2a arm and estimated using exact CIs based on the binomial distribution (Clopper-Pearson intervals) from the evaluable subjects for selected arms. All subjects treated in the study with data available for the calculation of the primary endpoint ORR will be considered evaluable. A test from the Simon minimax design for null hypothesis ORR proportion 4% vs alternative hypothesis 21% in the

arm population will be conducted in selected arms at 1-sided alpha = 0.025 and the p-value reported.

Arms I, II, III, IV, and V of the Phase 2a study stage will follow the Simon's two-stage minimax design. Each arm will enroll 17 evaluable subjects in Stage 1 and, if the Go/No Go criterion is met, an additional 8 evaluable subjects in Stage 2 will be enrolled for a total of 25 evaluable subjects/arm. This will provide an estimated 80% power per selected arm in the Phase 2a stage of the study for the primary hypothesis test using the Simon minimax design. Exact 95% binomial Clopper-Pearson CI estimates of ORR from each arm is planned to support the primary hypothesis tests.

Arms IVa, and Va of the Phase 2a study stage will not follow the Simon's two-stage minimax design.

Enrolment of up to 30 subjects per arm (I, II, III, IV, IVa, V, and Va) is planned to account for non-evaluable subjects and dropouts. Up to 238 subjects (up to 18 subjects in Phase 1b, up to 210 subjects in all arms of Phase 2a, and up to 10 subjects in the Biomarker Cohort) are planned to be enrolled in the study.

It has been reported that approximate 7% of pseudo-progression occurred in pembrolizumab monotherapy in patients with melanoma while comparing ORR assessed by RECIST 1.1 vs iRECIST (Hodi FS, 2016). This study will also explore the rate of pseudo-progression in NT-I7 plus pembrolizumab assessed by iRECIST.

In Phase 2a, Go/No Go decision for Arms I, II, III, IV, and V will be based on iRECIST, since iRECIST assessment starts after 1st progressive disease (PD) defined by RECIST 1.1.

2. GENERAL STATISTICAL CONSIDERATIONS

2.1 General Methods

Statistical analysis will be performed using SAS® software Version 9.4 or later.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (STD), median, minimum, and maximum. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data.

The estimated mean and median for a set of values should be calculated to one more decimal place than the raw (observed) data and rounded appropriately. Standard errors (or STDs) should be calculated to two decimal places beyond the raw (observed) data and rounded appropriately. Decimal place for minimum and maximum should be the same as raw (observed) data. Percentage values should be reported with one digit to the right of the decimal point. When numerator value is "0", it should be displayed as "0". Further, a maximum of 4 decimal places will be used for all summary statistics unless otherwise specified.

Summaries presented by visit will be based on the scheduled assessments as planned in the protocol. Unscheduled assessments will not be included in the by-visit summary tables,

however, will be included in the listings. The summary tables and listings will be presented as follows:

In Phase 1b: By DL and overall. The DLs are defined as:

- DL 1: NT-I7-480 μg/kg + pembrolizumab 200mg
- DL 2: NT-I7-960 μg/kg + pembrolizumab 200mg
- DL 3: NT-I7-1200 μg/kg + pembrolizumab 200mg

In Phase 2a: By dose expansion cohort defined as follows. All subjects in this phase will receive NT-I7 R2PD + Pembrolizumab 200mg.

- Arm I: CPI treated R/R TNBC
- Arm II: CPI treated R/R NSCLC
- Arm III: CPI treated R/R SCLC
- Arm IV: CPI naïve R/R MSS-CRC
- Arm IVa: CPI naïve R/R MSS-CRC
- Arm V: CPI naïve R/R PC
- Arm Va: CPI naïve R/R PC
- Biomarker Cohort: CPI naïve R/R OC

2.2 Definition of Baseline

Baseline value is defined as the last available value collected before the first dose of study drugs unless otherwise specified. If assessment time is collected, time should be compared as well.

2.3 Study Day

Study Day is relative to the first dose date of study drugs:

- If analysis date is on/after the date of first dose of study drugs, Study Day = analysis date – treatment start date +1.
- If analysis date is before the date of first dose of study drugs, Study Day = analysis date – treatment start date.

2.4 Study Visits

Study visits in EDC datasets include screen, C1D1, C1D2 C1D8, C2D1, C2D8, C2D15, C3D1, C3D8, C4D1, C5D1, C6D1, C6D15, …, CnD1, End of Treatment, safety follow ups, survival follow ups as well as unscheduled. The unscheduled study visits will not be recalculated for the analysis by visit, but the unscheduled visit values will be considered in the summary of worst change from baseline.

2.5 Coding Dictionaries

Medical history, medical or surgical procedures, and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.1.

Prior and concomitant medications will be coded using the WHO-Drug Dictionary September 2024 B3.

AEs and laboratory values will be graded with NCI CTCAE 5.0.

2.6 Stratified Analysis

No stratification is planned.

2.7 Testing Hypotheses

Arms I, II, III, IV, and V of the Phase 2a study stage will follow the Simon's two-stage minimax design. A test from the Simon minimax design for null hypothesis ORR proportion 4% vs. alternative hypothesis 21% in the arm population will be conducted in selected arms at 1-sided alpha = 0.025.

2.8 Handling of Missing Data

2.8.1 Handling of Partial Dates for Adverse Events

When determining the treatment-emergent adverse events (TEAEs), partial AE start and/or end dates will be handled as Table 1.

Table 1 Imputation Rules for Adverse Event Partial Dates

Date	Missing Part	Imputation Rule
Start Date	Missing Day	Assign first day of month unless it is the same month and year of the first dose of study drugs. Otherwise, assign date of first dose of study drugs or AE end date (if not missing), whichever is earlier.
	Missing Day, Month	Assign Jan 01 unless the year is year of first dose of study drugs. Otherwise, assign date of first dose of study drugs or AE end date (if not missing), whichever is earlier.
	Missing Day, Month, Year	Assign date of first dose of study drugs or AE end date (if not missing), whichever is earlier.
End Date	Missing Day	Assign the last date of the month or death date or data cut-off date (or end of study date), whichever is earliest.
	Missing Day, Month	Assign Dec 31 or death date or data cut-off date (or end of study date), whichever is earliest.
	Missing Day, Month, Year	If ongoing, end date is missing. Otherwise, assign death date or data cut-off date (or end of study date), whichever is earlier.

2.8.2 Handling of Partial Dates for Medications

When determining if a medication is a prior or concomitant medication, partial start and/or end date will be handled as Table 2.

Table 2 Imputation Rules for Medication Partial Dates

Date	Missing Part	Imputation Rule
Start Date	Missing Day	Assign first day of month unless it is the same month and year of the first dose of study drugs. Otherwise, assign date of first dose of study drugs or medication end date (if not missing), whichever is earlier.
	Missing Day, Month	Assign Jan 01 unless the year is year of first dose of study drugs. Otherwise, assign date of first dose of study drugs or medication end date (if not missing), whichever is earlier.
	Missing Day, Month, Year	Assign date of first dose of study drugs or medication end date (if not missing), whichever is earlier.
End Date	Missing Day	Assign the last date of the month or death date or data cut-off date (or end of study date), whichever is earliest.
	Missing Day, Month	Assign Dec 31 or death date or data cut-off date (or end of study date), whichever is earliest.
	Missing Day, Month, Year	If ongoing, end date is missing. Otherwise, assign death date or data cut-off date (or end of study date), whichever is earlier.

The imputed date will be used to categorized TEAEs and prior/concomitant medications. The data listings will report original data instead as the imputed date.

For incomplete dates involving efficacy and other safety data, a conservative imputation will be used for calculation if needed. More details of imputation rules will be specified in study analysis dataset specification.

2.9 Timing of Analysis

2.9.1 Interim Analysis

In Phase 1b there is a safety interim analysis after each DL to determine the dosing for the next subject.

In Phase 2a, Arms I, II, III, IV, and V will have a futility interim analysis per the Simon's two-stage minimax design at 17 evaluable subjects based on ORR assessed by iRECIST. If at least one subject achieves objective response (iCR or iPR) in an arm, that arm may be expanded by enrolling up to 8 evaluable additional subjects in Stage 2. Study enrollment will continue while the first 17 possible evaluable subjects are undergoing evaluation to confirm response. If no objective response is observed in an arm during Stage 1, further enrollment will be stopped in that arm.

In Phase 2a, Go/No Go decision for Arms I, II, III, IV, and V will be based on iRECIST, since iRECIST assessment starts after 1st PD defined by RECIST 1.1.

An interim analysis will not be performed for IVa, Va, and the Biomarker Cohort.

2.9.2 Final Analysis

Final analysis will be performed based on the data from electronic data capture (EDC) and vendors after database lock.

3. ANALYSIS SETS

3.1 Safety Analysis Set

The safety analysis set is defined as all subjects who received at least one dose (even partially) of one or both study medications. This analysis set will be used for all safety analysis.

3.2 DLT Evaluable Analysis Set

The DLT evaluable analysis set will consist of those subjects in Phase 1b portion of the study who are in safety analysis set and have completed the first 21 days (3 weeks) of study treatment (Cycle 1, Day 1 to 21) or any subjects who have not completed 21 days due to DLT.

3.3 Efficacy Evaluable Analysis Set

The efficacy evaluable analysis set will include all subjects who have received at least one dose of both the study medication (NT-I7 and Pembrolizumab) and have an evaluable baseline and at least one evaluable post-baseline assessment of tumor response.

This analysis set will be used as the primary analysis set for all efficacy analysis.

3.4 Per-Protocol (PP) Analysis Set

The PP analysis set is defined as all subjects who received at least one dose of both study medication (NT-I7 and Pembrolizumab), had at least one serum concentration, and did not have any important protocol deviations that potentially affect NT-I7 and Pembrolizumab metabolism.

The PP Set will be used for all PK analysis.

4. STATISTICAL METHODOLOGY

4.1 Study Subjects Disposition

Following information will be provided.

- Number of subjects screened and enrolled study
- Safety analysis set,

- DLT evaluable analysis set
- Efficacy evaluable analysis set
- Per Protocol (PP) analysis set
- Number and percentage of subjects who completed treatment
- Number and percentage of subjects who discontinued treatment
- Primary reason for discontinuation of treatment: Include the reasons being reported in EDC only. It will be categorized as 'Missing' if the reason is missing due to data issue.
  - AE
  - Dead
  - Lack of efficacy
  - Lost to follow-up
  - No longer clinically benefiting
  - Non-compliance with study schedule
  - Physician decision
  - Pregnancy
  - PD
  - Protocol deviation
  - Protocol-specified withdrawal criterion met
  - Recurrent disease
  - Study terminated by sponsor
  - Subject removed at sponsor request
  - Technical problem
  - Trial site terminated by sponsor
  - Withdrawal by subject
  - Other
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who discontinued the study
- Primary reason for study discontinuation: Include the reasons being reported in EDC only. It will be categorized as 'Missing' if the reason is missing due to data issue.
  - AE
  - Dead
  - Lack of efficacy
  - Lost to follow-up
  - No longer clinically benefiting
  - Non-compliance with study schedule
  - Physician decision
  - Pregnancy
  - PD
  - Protocol deviation
  - Protocol-specified withdrawal criterion met
  - Recurrent disease
  - Study terminated by sponsor
  - Subject removed at sponsor request

- Technical problem
- Trial site terminated by sponsor
- Withdrawal by subject
- Other

Subjects disposition data will also be presented in data listings.

4.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the clinical protocol. Protocol deviations will be classified by the sponsor or designee prior to primary analysis and important protocol deviations will be identified as those deviations from the study protocol that may significantly impact the completeness, accuracy, and/or reliability of the trial data; or that may significantly affect a subject's rights, safety, or well-being (ICH E3 R1 Guidelines 2013). Number and percentage of subjects with important protocol deviation will be summarised.

Protocol deviations will be listed.

4.3 Demography and Baseline Characteristics

Descriptive statistics, including number of subjects (n), mean, STD, median, minimum and maximum, will be used to summarize the following parameters:

- Age (years)
- Weight (kg) at Baseline
- Height (cm) at Baseline
- Body Mass Index (kg/m^2) at Baseline

The following demographic categories will be summarized with the number and percentage of subjects:

- Age Group (years): < 65, ≥ 65 to < 75, ≥ 75
- Gender: Male, Female, Undifferentiated, and Unknown
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown, and Other. The details of other ethnicities will be listed as appropriate.
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported, and Unknown. The details of other races will be listed as appropriate.

4.4 Disease History

The following disease history will be summarized with descriptive statistics (n, mean, STD, median, minimum and maximum) using safety analysis set:

- Time since initial diagnosis (Months) = (Date of first NT-I7 Dose - Date of initial Diagnosis)/30.4375
- Time since histopathologic diagnosis (Months) = (Date of first NT-I7 Dose - Date of histopathologic diagnosis)/30.4375

The following disease history categories will be summarized with the number and percentage of subjects:

- Type of cancer diagnosed (TNBC, NSCLC, SCLC, CRC (left side, right side, both side), PC, OC)
- Stage at diagnosis (1, 2, 3, 4)
- Substage at diagnosis (Alpha) (A, B, C, E, X, Bulky)
- Substage at enrollment (Alpha) (A, B, C, E, X, Bulky)
- T staging at enrollment (T0, T1, T2, T3, T4)
- N staging at enrollment (N0, N1, N2, N3)
- M staging at enrollment (M0, M1)
- Histopathology performed on primary tumor and metastatic site
- Eastern Cooperative Oncology Group (ECOG) Status at Baseline (0 or 1)

Baseline PD-L1 IHC expression and Immunohistochemical analysis results for available data in the arm performed will be listed.

In addition, below baseline characteristics (descriptive statistics for continuous variable or number/percentage for categorical variable) will be provided based on data as appropriate

- Liver metastasis at baseline (Yes)
- Subjects with liver metastasis at baseline: 0, 1, $\geqslant$ 2
- Sum of target lesions at baseline (mm): $\leqslant$ 100 mm, > 100 mm
- Absolute lymphocyte count (ALC): $\leqslant 10^3$/uL, $>10^3$/uL

4.5 Prior Systemic Anti-Cancer Therapy

Regimen Number will be summarized with descriptive statistics (n, mean, STD, median, minimum and maximum) using safety analysis set.

The following prior systemic anti-cancer therapy categories will be summarized with the number and percentage of subjects:

- Type of therapy (chemotherapy, hormonal therapy, biologic therapy, targeted therapy, other)
- Regimen number (1, 2, 3, $\geq$ 4)
- Therapy setting (adjuvant, conditioning, consolidation, induction, locally advanced, maintenance, metastatic, mobilization, neo-adjuvant, preventative, salvage)
- Best response at last regimen (CR, PR, SD, PD, Not Evaluable [NE], Unknown)
- Number of prior anti-cancer therapy: 0 ,1, 2, 3, 4, $\geq$ 5. Therapy setting of 'adjuvant', 'neo-adjuvant', 'maintenance' will be excluded from the number of prior anti-cancer therapy.

4.6 Medical History

System organ class (SOC) and preferred term (PT) of medical history will be coded with MedDRA 27.1. A subject will be counted only once within one PT if the subject reported

the same PT multiple times. The summary will be sorted by the frequency of SOCs and PTs in overall total.

Medical history information collected on "Medical History" case report form (CRF) page will be listed.

4.7 Prior and Concomitant Medications

All medications will be coded using the WHO-Drug Dictionary September 2024 B3.

Prior medications are all medications (prescription and over-the-counter [OTC]) taken within 30 days of Screening visit. Concomitant medications are all medications (prescription and OTC) taken between 7 days prior to Cycle 1, Day 1 through the Safety Follow-up visit (up to 30 days after the last dose of study treatment).

Prior and concomitant medications will be summarized by anatomical therapeutic classification (ATC) class (2nd level, chemical subgroup) and preferred name. A subject will only be counted once within each ATC-2 code and within each preferred name.

Prior and concomitant medications will also be presented in data listings.

4.8 Exposure of NT-I7 and Pembrolizumab

Exposure for NT-I7 and pembrolizumab will be summarized separately using safety analysis set by DL or arm depending on the study phase presented.

The exposure summary of NT-I7 and Pembrolizumab will be presented (descriptive statistics for continuous variables and number of subjects/percentages for categorical variables) for the following:

- Number of doses received
- NT-I7 treatment duration (weeks) = (date of last dose – date of first dose + 43)/7.
- Pembrolizumab Treatment duration (weeks) = (date of last dose – date of first dose + 22)/7.
- Cumulative Dose (mg) = Sum (actual dose per administration (mg))
- Average Dose per Cycle (mg/cycle) = Sum (actual dose per administration (mg))/number of treatment cycle started
- NT-I7 average actual dose per administration (ug/kg) = Sum (actual dose per administration (mg)*1000/weight)/number of doses received
- Pembrolizumab average actual dose per administration (mg) = Sum (actual dose per administration (mg)/number of doses received
- NT-I7 Treatment compliance (%) = (Sum (total dose administered (mg))/Sum (dose per administration planned(ug/kg)*weight (kg)/1000)) *100
- Pembrolizumab Treatment compliance (%) = (Sum (total dose administered (mg))/ sum (dose per administration planned(mg)))*100
- Number of subjects with at least one dose not administered with a breakdown of reasons for dose not taken

- Number of subjects with at least one dose adjustment with a breakdown of reasons for dose adjustment.
- Number of subjects with at least one infusion interruption with a breakdown of reasons for infusion interruption (Pembrolizumab only).

All study drug exposure data will be listed.

4.9 Efficacy Analysis

All efficacy analysis will be summarized by DL or arm for each phase primarily based on efficacy evaluable analysis set.

4.9.1 Tumor Assessment and Overall Visit Response

Initial tumor imaging at Screening must be performed within 28 days prior to the date of treatment. The first on-study imaging assessment should be performed at 6 weeks (±1 week) from the date of the first study treatment. Subsequent tumor imaging should be performed every 6 weeks (±1 week) or more frequently if clinically indicated. After the first 6 months, subjects who remain on treatment will have imaging performed every 9 weeks (±1 week). Imaging should continue to be performed until disease progression is identified by the investigator, or notification by the Sponsor, whichever occurs first.

Target lesion response, non-target lesion response, and overall response of each visit will be reported by investigator according to RECIST 1.1 criteria and iRECIST criteria in protocol Appendix A.

The RECIST 1.1 assessment has the following possible response categories: CR, PR, SD, PD or NE.

The iRECIST criteria is similar to RECIST 1.1 but requires an evaluation of PD to be confirmed at subsequent assessment. For purposes of iRECIST assessment, the first visit showing PD according to RECIST 1.1 will be assigned as immune-unconfirmed PD (iUPD) at this visit. On a subsequent confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD, see protocol Appendix A for the confirmation rules for iCPD). The iRECIST assessment has the following possible response categories: iCR, iPR, immune-Stable Disease (iSD), iUPD, iCPD, and NE.

4.9.2 Best Overall Response

BOR will be derived based on all overall visit response per subject.

4.9.2.1 Best Overall Response per RECIST 1.1

The derivation rules of confirmed response in table 3 are listed for RECIST 1.1.

Table 3 Derivation of Confirmation of Response from Timepoint Overall Response

Response at First Time Point	Response at Subsequent Time Point	BOR with Confirmation per RECIST 1.1
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD or PD	SD provided minimum criteria[b] for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria[b] for SD duration met, otherwise NE
PR	CR or PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria[b] for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria[b] for SD duration met, otherwise NE

BOR = best overall response; CR = complete response; PR = partial response; SD = stable disease, PD = progressive disease; NE = not evaluable.
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best confirmed response is PR.
[b] Minimum criteria for SD duration is 4 weeks.

A BOR of CR or PR must be confirmed by a tumor assessment that should be performed no less than 4 weeks after the criteria for response are first met. One intervening response SD is allowed for PR confirmation (PR SD PR=PR; PR SD CR=PR if confirmed CR is not achieved).

4.9.2.2 Best Overall Response per iRECIST

BOR will be derived based on all overall visit response per subject. The iRECIST assessment has the following possible response categories: iCR, iPR, iSD, immune-Unconfirmed PD (iUPD), immune-Confirmed PD (iCPD) or immune-Not Evaluable (iNE). The iRECIST criteria is similar to RECIST v1.1 but for PD, iRECIST requires an evaluation of PD to be confirmed at subsequent assessment. For purposes of iRECIST assessment, the first visit showing PD according to RECIST v1.1 will be assigned as Immune-Unconfirmed PD (iUPD) at this visit. Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

BOR (when confirmation required) per iRECIST will be derived as follows:

- BOR follows the same rules as table 3 per RECIST for confirmation of iCR/iPR, and iSD (meet the minimum criteria), except PD in column response at subsequent

timepoint in table 3 per RECIST is considered as iUPD and should be confirmed by iCPD.

- BOR of iPD (iCPD>iUPD):
  - If subjects did not meet BOR of iCR/iPR, and iSD, BOR for iCPD (time point iUPD must be confirmed by timepoint iCPD no less than 4 weeks per iRECIST) can be achieved as order of iUPD followed by iCPD without interruption of iCR, iPR, iSD.
  - If above scenarios are not achieved, BOR is identified as iUPD.
- BOR of NE refers to no baseline or no postbaseline assessments or all postbaseline assessments are NE.
- BOR of Unknown refers to unconfirmed iCR/iPR or early iSD <4 weeks from first dose date.

4.9.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint for Phase 2a is the ORR per RECIST 1.1 and iRECIST as determined by the Investigator.

ORR per RECIST 1.1 is defined as the proportion of subjects with confirmed CR or confirmed PR as BOR in efficacy evaluable analysis set.

iORR per iRECIST is defined as the proportion of subjects with iCR or iPR as BOR in efficacy evaluable analysis set.

Exact two-sided 95% CIs for the ORR/iORR will be calculated using Clopper-Pearson method.

A test from the Simon minimax design for null hypothesis ORR/iORR proportion 4% vs alternative hypothesis 21% will be conducted in each Phase 2a Arm: Arm I, II, III, IV, IVa, V, and Va at 1-sided alpha = 0.025 and the p-value reported.

4.9.4 Secondary Efficacy Endpoints Analysis for Phase 1b/2a/Biomarker Cohort

4.9.4.1 Objective Response Rate per RECIST 1.1 and iRECIST as determined by the Investigator for Biomarker Cohort

The same definition is followed as that for primary endpoint.

Exact two-sided 95% CIs for the ORR/iORR will be calculated using Clopper-Pearson method.

In addition, the following figures will be provided for each phase/arm, as applicable.

- Waterfall plot for best percentage change of target lesion size from baseline (maximum decrease, or minimum increase if no decrease)
- Swimmer plot for treatment duration and response
- Spider plot for the change of target lesion from baseline

4.9.4.2 Disease Control Rate per investigator

DCR per RECIST 1.1 is defined the proportion of subjects with confirmed CR, confirmed PR, SD (minimum duration of 4 weeks from the first dose of study drugs to the date of last non PD/NE) as BOR in efficacy evaluable analysis set.

iDCR per iRECIST is defined the proportion of subjects with iCR, iPR, iSD as iBOR in efficacy evaluable analysis set.

Exact two-sided 95% CIs for the DCR/iDCR will be calculated using Clopper-Pearson method.

4.9.4.3 Duration of Response and Progression Free Survival per investigator

DoR per RECIST 1.1

For subjects who achieve confirmed CR or PR as BOR, DoR is defined as the time (months) from the date of the first CR/PR to the date of the documented disease progression or death, whichever occurs first. The subjects without progression and alive will be censored according to censor rule.

Censoring rules for DoR are the same as those of PFS (Table 4).

iDoR per iRECIST

For subjects who achieve iCR or iPR as BOR, iDoR is defined as the time (months) from the date of the first iCR/iPR to the date of the first iUPD that is followed by iCPD without interruption by iSD/iPR/iCR or death, whichever occurs first. The subjects without iCPD and alive will be censored on the date of last assessment (including iUPD). Censoring rules for DoR are the same as those of PFS (Table 5).

DoR/iDoR median values and its two-sided 95% CIs will be estimated using Kaplan-Meier (KM) method. The DoR/iDoR event-free rates at 3 and 6 months if applicable and the associated two-sided 95% CIs will also be estimated using KM method.

Progression free survival (PFS) per RECIST 1.1

PFS is defined as the time (months) from the date of the first dose of study drugs to the date of the documented disease progression or death, whichever occurs first. The subjects without progression and alive will be censored on the date of last assessment.

Progression free survival (PFS) per iRECIST

iPFS is defined as the time (months) from the date of the first dose date of study drugs to the date of the first iUPD that is followed by iCPD without interruption by iSD/iPR/iCR or death, whichever occurs first. The subjects without iCPD and alive will be censored on the date of last assessment (including iUPD).

PFS/iPFS median values and its two-sided 95% CIs will be estimated using KM method. The PFS/iPFS event-free rates at 3 and 6 months if applicable and the associated two-sided 95% CIs will also be estimated using KM method.

PFS/iPFS of each DL in Phase 1a and each arm in Phase 2a will be plotted with KM curve.

Table 4 Censoring and Event rules for DoR and PFS per RECIST 1.1

Situation	Date of Progression or Censoring	Outcome
No PD or death at the time of data cutoff	Date of last adequate disease assessment	Censored
Start a new anti-cancer therapy before death or PD	Date of last adequate disease assessment prior to the date of new anti-cancer therapy	Censored
Death or PD after two or more missing consecutive assessments	Date of last adequate disease assessment before missing two or more consecutive assessments	Censored
1 missed disease assessments before Death or PD	Date of Death or PD, whichever is first	Event
Death or PD before or no new anti-cancer therapy	Date of Death or PD, whichever is first	Event

Table 5 Censoring and Event rules for iDoR and iPFS per iRECIST

Situation	Date of Progression or Censoring	Outcome
No iCPD or death at the time of data cutoff	Date of last adequate disease assessment	Censored
Start a new anti-cancer therapy before death or iCPD	Date of last adequate disease assessment prior to the date of new anti-cancer therapy	Censored
Death or iCPD after two or more missing consecutive assessments	Date of last adequate disease assessment before missing two or more consecutive assessments	Censored
1 missed disease assessments before death or iCPD	Date of the (1) first iUPD that is followed by iCPD without interruption by iSD/iPR/iCR, (2) date of iCPD if no immediate prior iUPD, or (3) death, whichever occurs first	Event
Death or iCPD before/ or no new anti-cancer therapy	Date of the (1) first iUPD that is followed by iCPD without interruption by iSD/iPR/iCR, (2) date of iCPD if no immediate prior iUPD, or (3) death, whichever occurs first	Event

All efficacy data including target/non-target/new lesions measurement will be listed.

4.9.4.4 Overall Survival

Overall survival (OS) is defined as the time (months) from the date of the first dose date of study drugs to the date of death. Subjects who are alive will have their OS time censored at the last known alive date. The last known alive date will be derived based on the assessment dates that are reported in all CRFs, except for CRFs being used at screening.

OS median values and its two-sided 95% CIs will be estimated using KM method. The OS event-free rates at 6 and 12 months if applicable and the associated two-sided 95% CIs will also be estimated using KM method.

OS of each DL in Phase 1b and each arm in Phase 2a will be plotted with KM curve.

4.10 Subgroup analysis

Based on the data availability, ORR, DoR, DCR, PFS, and OS of Phase 2a arms might be analysed with following subgroups:

- Number of prior anti-cancer therapy: 0 ,1, 2, 3, 4, ≥ 5. Therapy setting of 'adjuvant', 'neo-adjuvant', 'maintenance' will be excluded from the number of prior anti-cancer therapy
- Number of lesions in liver at baseline: 0, 1, ≥ 2
- Baseline sum of target lesion: ≤ 100 mm, > 100 mm
- Baseline absolute lymphocyte count (ALC): $\leq 10^3$/uL, $> 10^3$/uL
- Age (year): < 65, ≥ 65 to < 75, ≥ 75
- Location of CPI naïve R/R MSS-CRC (Rectum, Colon, Other)

4.11 Safety Analysis

Safety analysis will be summarized by Phase 2 arms and by dose group for dose Phase1b based on safety analysis set unless otherwise specified.

For safety shift tables, schedule and unscheduled measurements up to 30 days after last dose date will be included in worst postbaseline results derivation.

4.11.1 Dose-limiting Toxicities

All toxicities will be graded using NCI-CTCAE Version 5.0. For the purpose of this study, a DLT is any event attributed to NT-I7 and/or to pembrolizumab and occurring during the DLT period of first 21 days.

DLT is defined as any AE occurring within the first 21 days (i.e., Cycle 1, Day 1 through Day 21), that is considered to be at least possibly, probably, or definitely related to the study treatment (NT-I7 and/or pembrolizumab) per the investigator, and that meets at least one of the non-hematologic or hematologic criteria listed below.

- Grade 4 non-hematologic toxicity (not laboratory).
- Grade ≥ 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheal per standard of care
- Grade ≥ 3 rash, lasting ≥ 5 days
- Grade 4 neutropenia, lasting ≥ 5 days
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as absolute neutrophil count (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.
- Other Grade 4 hematologic toxicity lasting ≥ 7 days, except thrombocytopenia:
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia associated with clinically significant bleeding

Note: Peripheral lymphocytopenia after the first NT-I7 injection is not a sign of toxicity; it reflects the lymphocytes "homing effect" of NT-I7. Lymphocyte counts usually come back to baseline 5 to 7 days after the first injection.

- Any non-hematologic AE ≥ Grade 3 in severity should be considered a DLT, with the following exception: Grade 3 fatigue lasting ≤ 3 days.; without use of corticosteroids or anti-inflammatory agents per standard of care.
- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
  - Clinically significant medical intervention is required to treat the subject, or
  - Abnormality leads to hospitalization, or
  - The abnormality persists for > 1 week, or
  - The abnormality results in potential Drug-induced Liver Injury (DILI) as defined by Hy's Law.

  Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- Other Grade ≥ 3 clinical laboratory abnormalities must be reversible to ≤ Grade 1 within 72 hours with outpatient care and/or monitoring AND must not be considered clinically significant by the treating physician to be excluded from the definition of DLT.
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Grade 5 toxicity.

DLTs in each cohort of dose escalation (Phase 1b) will be coded using MedDRA version 27 .1 and will be summarized by SOC and PT using DLT analysis set.

DLTs will also be displayed in a data listing.

4.11.2 Adverse Events

AE will be coded using MedDRA version 27.1 and graded using the NCI-CTCAE version 5.0.

A TEAE is any AE that starts on/after the first day of study treatment or that worsens on/after the first day of study treatment, and up to 30 days (90 days for serious adverse events [SAEs]) after the date of last dose of study drugs, or initiation of new anticancer therapy, whichever is earlier.

For the purpose for regulatory reporting, relationships of "definite", "probable" and "possible" to study drug as assessed by the investigator will be defined as related to study treatment. Missing relationship will not be imputed.

Adverse events of special interest (AESIs) in NT-I7 are defined in protocol section 11.4. Events of clinical interest (ECI) in pembrolizumab are defined in protocol section 11.6.

An overall summary of TEAEs using frequencies and percentages of subjects will be presented based on the following categories:

- TEAEs
- NT-I7-related TEAE
- Pembrolizumab-related TEAE
- Either NT-I7 or pembrolizumab-related TEAE
- TEAEs with Grade 3 or higher
- NT-I7-related TEAE with Grade 3 or higher
- Pembrolizumab-related TEAE with Grade 3 or higher
- Either NT-I7 or pembrolizumab-related TEAE with Grade 3 or higher
- Serious TEAE
- NT-I7-related serious TEAE
- Pembrolizumab-related serious TEAE
- Either NT-I7 or pembrolizumab-related serious TEAE
- TEAEs leading to NT-I7 interrupted/held
- TEAEs leading to NT-I7 dose reduced
- TEAEs leading to NT-I7 permanently withdrawn
- TEAEs leading to pembrolizumab interrupted/held
- TEAEs leading to pembrolizumab permanently withdrawn
- TEAEs leading to discontinuation from the study
- AESI in NT-I7
- ECI in pembrolizumab
- TEAEs considered injection site reaction (ISR)
- TEAEs considered infusion-related reactions (IRR)
- TEAEs leading to death

The above events will be tabulated by SOC and PT. SOC will be sorted by descending frequency and then alphabetically for ties. Within each SOC, PT will also be sorted by descending frequency and then alphabetically for ties, by the overall number of subjects in Phase 1b/Phase 2a total. If a PT is reported more than once for a subject, the subject will only be counted once in the incidence for that PT.

The following events will be tabulated by SOC, PT, and maximum CTCAE grade. SOC will be sorted by descending frequency and then alphabetically for ties. Within each SOC, PT will be sorted by descending frequency and then alphabetically for ties, by the overall number of subjects.

- TEAEs
- NT-I7 -related TEAE
- Pembrolizumab-related TEAE
- Either NT-I7 or pembrolizumab-related TEAE

Summaries of events by decreasing frequency of PT include:

- TEAEs
- NT-I7 Related TEAE

- Pembrolizumab Related TEAE
- Serious TEAE
- NT-I7 Related Serious TEAE
- Pembrolizumab Related Serious TEAE

If a PT is reported more than once for a subject, the subject will only be counted once in the incidence for that PT.

The following listings will be provided:

- All AEs (flag TEAE)
- SAEs (flag TEAE)
- TEAEs leading to NT-I7 interrupted/held
- TEAEs leading to NT-I7 permanently withdrawn
- TEAEs leading to NT-I7 dose reduced
- TEAEs leading to pembrolizumab interrupted/held
- TEAEs leading to pembrolizumab permanently withdraw
- AESI in NT-I7
- ECI in pembrolizumab
- TEAEs leading to death
- TEAEs considered ISR
- TEAEs considered IRR
- TEAEs leading to death

4.11.3 Clinical Laboratory Evaluation

Hematology, serum chemistry, coagulation, thyroid function test, and urinalysis tests are listed in table 6.

Table 6 Clinical Laboratory Tests

Chemistry	Hematology
Alanine aminotransferase (ALT)/ serum glutamate pyruvic transaminase (SGPT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST); serum glutamic oxaloacetic transaminase (SGOT) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine Direct bilirubin Glucose Indirect bilirubin Lactate dehydrogenase (LDH) Magnesium	Red blood cell (RBC); Erythrocyte Hemoglobin Hematocrit White blood cell (WBC); Leukocytes Neutrophils (Absolute) Neutrophils band form (Absolute) Lymphocytes (Absolute) Monocytes (Absolute) Eosinophils (Absolute) Basophils (Absolute) Neutrophils/Leukocytes (%) Neutrophils band form/Leukocytes (%) Lymphocytes/Leukocytes (%) Monocytes/Leukocytes (%)

Phosphate Potassium Protein Sodium Total bilirubin (TBL) Urate (Uric Acid) Urea	Eosinophils/Leukocytes (%) Basophils/Leukocytes (%) Platelets
Coagulation	**Urinalysis**
Activated partial thromboplastin time (aPTT) International normalized ratio (INR) Prothrombin time (PT)	pH Specific Gravity Bilirubin Glucose Ketones
Thyroid function test	Leukocyte esterase
Thyroid stimulating hormone (TSH) Thyroxine, free (Free T4) Triiodothyronine (Total T3) Triiodothyronine, free (Free T3)	Nitrite Occult blood Protein Urobilinogen

Absolute value, change from baseline, and percentage change from baseline for continuous parameters (analytes) of hematology, serum chemistry, coagulation, and thyroid function tests will be summarized by visit and DLs/arm in each phase using descriptive statistics (mean, median, STD, minimum, maximum, and number of subjects).

Baseline and post-baseline hematology, serum chemistry, and coagulation tests will be classified as Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 based on CTCAE v5.0. Shift of these tests from baseline CTCAE grade to the worst postbaseline CTCAE grade will be presented by DLs/arm in each phase using the number and percentage of subjects at each shift category. If applicable, some laboratory tests have two CTCAE grade directions: hypo and hyper, where both directions will be presented in the shift table.

Proteinuria determined by dipstick shift from baseline to worst postbaseline will be provided if applicable. Thyroid function tests shift from baseline to worst postbaseline will be provided using normal, abnormal (not clinically significant) and abnormal (clinically significant)

The liver function tests (ASL, ALT, ALP, and TBL) will be summarized in the following worst postbaseline categories:

- AST3 x upper limit of normal (ULN)
  - 3 x upper limit of normal (ULN)
  - 5 x ULN
  - 10 x ULN
  - 20 x ULN
- ALT
  - 3 x ULN
  - 5 x ULN
  - 10 x ULN

  - 20 x ULN
- AST or ALT
  - 3 x ULN
  - 5 x ULN
  - 10 x ULN
  - 20 x ULN
- TBL
  - 1.5 x ULN
  - 2 x ULN
- ALP
  - < 2 ULN
- (AST or ALT) and TBL
  - AST or ALT ≥ 3 x ULN and TBL ≥ 2 x ULN
- (AST or ALT) and ALP and TBL
  - AST or ALT ≥ 3 x ULN and ALP < 2 x ULN and TBL ≥ 2 x ULN

Subjects meet below conditions will be listed if data is applicable:

- ALT or AST ≥ 3 x ULN
- TBL ≥ 2 x ULN
- ALP < 2 x ULN

All the laboratory values and CTCAE grades (if applicable) will be presented in data listings.

All laboratory tests will be presented in data listings.

Pregnancy test will be presented in data listing.

4.11.4 Vital Signs

All vital signs (height, weight, body temperature, respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure) will be assessed according to Protocol 7.4 - schedule of assessments.

Actual value, change from baseline, and percent change from baseline at each visit (timepoint if applicable) will be presented using descriptive statistics by DLs/arm in each phase.

All vital signs data will be presented in a data listing.

4.11.5 12-Lead Electrocardiograms

Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS duration, QT interval, corrected QT interval [QTc]B, and QTcF) will be assessed according to Protocol 7.4 - schedule of assessments.

Actual value, change from baseline, and percent change from baseline at each visit (timepoint if applicable) will be presented using descriptive statistics by DLs/arm in each phase.

The QTcF interval will be summarized by the frequencies of subjects with absolute value and/or change from baseline using the criteria identified below:

- ≤450
- >450 - 480
- >480 - 500
- >500
- ≤ 30 increases from baseline
- 30 to ≤ 60 increases from baseline
- > 60 increases from baseline

Subjects with abnormal ECG results, regardless of clinical significance, will be identified in data listings with flags for abnormalities.

4.11.6 Eastern Cooperative Oncology Group Performance Status

ECOG will be summarized over time as categorical variable and a shift table from baseline to worst post baseline will be provided.

All ECOG data will be presented in a data listing.

4.11.7 Physical Exam

Physical exam data will be presented in a data listing.

4.12 Biomarkers

A number of biomarkers will be assessed during the conduct of the study, including number, distribution, and phenotype of TILs, PD-L1 expression, and changes in TME.

TIL markers may include CD4, CD8, PanCK, and nuclear stain, among others. All TIL parameters (in vendor data of not listed here), PD-L1 expression, TME biomarkers will be summarized descriptively pre- and post-treatment in each arm by responder (CR or PR) vs. non-responder and PD vs. non-PD per RECIST and iRECIST, using the safety analysis set.

All biomarker results will be listed.

4.13 Immunogenicity

Samples for immunogenicity assays shall be collected pre-dose from all study subjects in Phase 1b, Biomarker Cohort, and up to 10 subjects in each of the arms of Phase 2a. Samples shall be collected pre-dose on C1D1, C2D1, C3D1, and C5D1. Thereafter, samples shall be collected pre-dose on every 4 cycle such as C9D1, C13D1, C17D1, C21D1, and so on.

Incidence of ADA to NT-I7 during the study will be assessed, relative to the prevalence of ADA at baseline. Immunogenicity to NT-I7 will be measured using a risk-based, tiered testing approach. This includes screening and confirmatory assays for binding ADAs, epitope-specific assays to characterize ADA reactivity to whole NT-I7 vs IL-7 domain, and a cell-based neutralizing ADA assay for IL7 bioactivity. Subject samples will be obtained

at baseline and over the course of treatment (to evaluate the prevalence and incidence of treatment-emergent/boosted ADA).

ADA will be summarized in tabular by the following categories:

- N (%) of subjects with ADA positive at baseline (i.e. ADA detectable in the C1D1 pre-dose sample)
- N (%) of subjects with ADA negative at baseline (i.e. ADA detectable in the C1D1 pre-dose sample)
- N (%) of subjects with post-dose ADA positive (i.e. ADA detectable in any pre-dose sample from Cycle 2 onward)
- N (%) of subjects with treatment-emergent ADA, defined as those subjects with a negative ADA result at baseline and one or more post-treatment (Cycle 2 onward) ADA-positive samples.
- Subjects with treatment-boosted ADA, defined as subjects with a positive baseline ADA result who had one or more post-treatment (Cycle 2 onward) ADA result with the titer increased at least 4-fold.

NT-I7 ADA at each visit will be summarized by timepoint, DL/arm of each phase using Safety Analysis Set.

4.14 Pharmacokinetics

The PP Set will be used for all PK analysis.

4.14.1 Serum Concentrations

PK timepoints for NT-I7 are listed in protocol Table 3.

Serum concentrations of NT-I7 below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values. Descriptive statistics (number of subjects, mean, geometric mean, STD, coefficient of variation (CV), median, min, and max) will be used to summarize the serum concentrations by DL in Phase 1b and by arm in Phase 2a at each scheduled timepoint.

Linear (+/-STD) and semi-logarithmic (+/-STD) plots of the arithmetic mean serum concentration by scheduled sampling time will be provided by DL in Phase 1b and by arm in Phase 2a. These plots will show time in hours. The plots will present all calculated means and will include a reference line for lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual serum concentration by actual sampling time will be provided by DL in Phase 1b and by arm in Phase 2a.

All individual subject serum concentration data will be listed by subject, by phase and by DL in Phase 1b and by arm in Phase 2a.

Cycle 1 Day 8 pre-dose will be assigned as 168 hour post-dose on Cycle 1 Day 1, Cycle 2 Day 1 pre-dose will be assigned as 504 hour post-dose on Cycle 1 Day 1 and Cycle 3 Day 1 pre-dose was assigned as 1008 hour post-dose on Cycle 1 Day 1.

4.14.2 Pharmacokinetic Parameters

Serum PK parameters for NT-I7 will be estimated using non-compartmental methods with WinNonlin® version 8.1 using best fit regression. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. In estimating the PK parameters, BQL values will be set to zero. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

The serum concentration of NT-I7 administered in combination with pembrolizumab will be collected at specified study timepoints. The PK parameters (Table 7) will be calculated as applicable for each subject:

Table 7 PK Parameters

Parameter	Description
C_{max}	Maximum serum concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units
C_{min}	Observed plasma concentration at the end of each dosing interval (C_{min} Cycle X, Day Y)
T_{max}	Time to maximum serum concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.
AUC_{last}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time zero to infinity. $AUC_{0\text{-}inf} = AUC_{last} + C_{last}/Lz$ where C_{last} is the last observed quantifiable concentration and λz is the terminal phase rate constant.
$T_{1/2}$	Terminal elimination phase half-life expressed in time units.
CL/F	Apparent clearance after extra-vascular dose.
Vz/F	Apparent volume of distribution

Additional PK parameters might be calculated as necessary based on the emergent data. Any resulting modification will be documented in CSR. The sampling time post T_{max} might not be adequate to estimate the terminal phase and calculate parameters as CL/F, Vz/F, $T_{1/2}$ and $AUC_{0\text{-}inf}$, therefore the final analysis will be based on the evaluable data concentration-time data.

Descriptive statistics (number of subjects, mean, geometric mean, STD, % CV, median, min, and max) will be used to summarize the calculated PK parameters by DL in Phase 1b and by arm in Phase 2a. For T_{max}, only median, min and max will be presented.

All parameters will be listed by subject.

5. INTERIM ANALYSIS

In Phase 2a, Arms I, II, III, IV, and V will have futility interim analysis per the Simon's two-stage minimax design at 17 evaluable subjects based on ORR assessed by iRECIST. If at least one subject achieves objective response of iCR or iPR in an arm per iRECIST, that arm may be expanded by enrolling up to 8 evaluable additional subjects in Stage 2. Study enrollment will continue while the first 17 possible evaluable subjects are undergoing evaluation to confirm response. If no objective response is observed in an arm during Stage 1, further enrollment will be stopped in that arm.

In Phase 2a, Go/No Go decision for Arms I, II, III, IV, and V will be based on iRECIST, since iRECIST assessment starts after 1st PD defined by RECIST 1.1.

In interim analysis, the analyses below will be performed based on statistical methods and procedure described in the SAP.

- Subject disposition
- Demographic and disease history
- Prior systemic anti-cancer therapy
- Summary of exposure of NT-17 and pembrolizumab
- ORR per RECIST 1.1 and iRECIST
- DoR per RECIST 1.1 and iRECIST
- KM plot for DoR, PFS and OS per iRECIST 1.1
- Swimmer plot/waterfall plot/spider plot
- Subgroup analysis for ORR/DoR/PFS/OS per iRECIST 1.1
- TEAE/Related TEAE/SAE by SOC/PT/Maximum CTCAE grade
- TEAE of special interest of NT-I7/ ECI of pembrolizumab by PT/Maximum CTCAE grade
- Lab parameter figure for ALC: Change from baseline (Mean ± Std) and mean percentage change from baseline over time

Additional analysis maybe be performed if needed.

6. CHANGES FROM ANALYSIS PLANNED IN THE PROTOCOL

Analysis is added:

- Exploratory analysis of pre- and on-treatment tumor biopsy samples from the same organ will be performed and compared between responders vs. non-responders and PD vs. non-PD to help elucidate changes in TILs, PD-L1 expression, and TME biomarkers that may be correlated with treatment response.

Analyses are excluded:

- Expression of IFN-γ and associated inflammatory gene expression in the TME.
- Changes in peripheral blood biomarkers, including but not limited to immunophenotyping and inflammatory mediators, will be analyzed in association with 1) the incidence of AEs and 2) as surrogated markers of response, TME changes and TIL infiltration.

7. REFERENCES

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