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

NCT Number: NCT04332653

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NEOIMMUNETECH

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

Protocol Number:	NIT-110 (KEYNOTE A60)
Version:	v7.0 (incorporating Amendment 6)
Products:	NT-I7 (also known as efineptakin alfa, rhIL-7-hyFc) Pembrolizumab
Abbreviated Title:	NT-I7 (efineptakin alfa) in Combination with Pembrolizumab in Advanced Solid Tumors
Study Phase:	Phase 1b/2a
IND Number:	146869
IND Sponsor:	NeoImmuneTech, Inc. 2400 Research Blvd, Suite 250 Rockville, MD 20850 NIT110@neoimmunetech.com www.neoimmunetech.com
Date of Protocol:	26 Oct 2023

Sponsor Signatory

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted]

Sponsor (print name)

[redacted]

Title

[redacted]

26 Oct 2023

Date (dd-mmm-yyyy)

Signature of Investigator

Protocol 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
Protocol Number:	NIT-110 (KEYNOTE A60)
Version:	v7.0, dated 26 October 2023

This protocol is a confidential communication of NeoImmuneTech, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy by e-mail to NIT110@neoimmunetech.com

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Protocol Revisions

Version	Date	Revisions
1.0	03 Dec 2019	--
2.0	04 Feb 2020	Amendment#1 (Summary of Changes) • Added a third dose level (1200 µg/kg IM Q6W) if safety will permit, per recommendation from FDA. • With the additional dose level, number of subjects in the Phase 1b has been increased from up to 12 to up to 18. Total number of subjects in the study increased from up to 162 to up to 168. • Study design and treatment schema have been changed to introduce new dose level and more subjects. • Provided examples of dose levels for dose de-escalation if needed. • Rationale for dose selection has been updated to provide justification for the higher dose. • Provided more clarity on endpoint correlation for the primary objectives. • Objective and endpoints now have the descriptive methodology and statistical analysis details. • NT-I7 pharmaceutical information and name of active ingredient have been updated for consistency with vial label. • Storage and handling instructions of NT-I7 have been updated. • Updated DLT criteria per FDA recommendations. • PK will be collected from all subjects in Phase 1b and Phase 2a, per FDA recommendation. Earlier PK was planned only for subjects in Phase 1b. Hence, Table 5 has been modified accordingly. • Immunogenicity sample collection: Additional collection of pre-dose C2D1 has been newly added. Frequency of collection after cycle 5 have changed to every 4 cycles. Sample collection will be done in all Phase 1b, and in up to 10 subjects per arm in Phase 2a. Section 7.4 Schedule of Assessments have been modified accordingly. • Additional blood sample collection for TCR seq analysis have been added to go with corresponding biopsy-mandated subjects. • PK assessment in the Schedule of Assessments mentions to refer to Table 5. • Section 9 under concomitant therapy has been divided into two sections 9.1 – Prohibited Medications/Treatment and 9.2 – Medications Used with Caution. • Information on QT/QTc drugs have been clarified and moved under Section 9.2.

		• Second biopsy have been clarified to indicate on-treatment biopsy in Section 12.1. Additional mention on the CD4+ and TCR repertoire analysis has been added. • Sample size and power calculation updated to reflect increased number of subjects. • DSMC meeting frequency, and updated information has been provided in Section 15.4. Statistical analysis plan summary has been updated. Secondary end point details have been updated. <u>Administrative Changes</u> • Protocol Number changed from NIT-110/PNA60 to NIT-110 (PNA60). • Changed version number and date. • Added IND number. • Added study specific email ID. • Mention of MK-3475 IB has been changed to Pembrolizumab IB. • Expedited AE reporting (Section 11.3) email and phone number have been updated. • Data management and reporting in Section 14, has been updated providing the term Site Operations Manual, instead of Study Procedures Manual. Study Oversight information has been clarified. Subject enrollment and EDC information updated to refer to the EDC Completion Guidelines.
3.0	01 Jun 2021	• Removed the alternate name for NT-I7, Hyleukin-7. • Included the International Nonproprietary Name for NT-I7, efineptakin alfa. • Provided clarification on the Exclusion criterion # 2 for prior treatment washout. • Updated section 2.4.1.2.3 to include recent studies under the NT-I7 clinical development program. • Included additional pharmacokinetic assessment timepoints. • Provided additional clarification on dose modifications to manage AEs. • Provided clarification on medications that should be used with caution while on treatment. • Updated reporting criteria for AESI reporting to Sponsor and safety designee. • Provided clarification on MRI brain imaging conduct. • Updated dose modification and toxicity management of immune-related AEs associated with NT-I7 and pembrolizumab.

		• Provided clarification on dose interruption for pembrolizumab and removed inconsistencies in duration of treatment interruptions due to nontreatment-related events or unforeseen circumstances. • Incorporated dose modification guidance to address recent pembrolizumab safety communications. • Included clarification on clear communication of timing of reporting of ECI from site to Sponsor. • Included Biomarker Cohort to study design in subjects with CPI naïve R/R ovarian cancer. • Updated reporting criteria for SAE for clarity. • Updated Appendix A • Clarification on enrolment during interim analysis at the end of Stage I. • Removed reference to a Table 8
4.0	26 Jul 2021	<u>Amendment #3 (Summary of Changes)</u> • Primary endpoint updated to iRECIST. • Applicable updates to iRECIST and RECIST throughout the document. • Rationale of amending iRECIST added in the statistical section. • iRECIST updated in the Appendix. • References updated as applicable.
5.0	17 Mar 2022	• Updated header from “KEYNOTE A60” to “KEYNOTE PNA60” • Updated 178 subjects to 238 subjects • Clarified that Arms I, II, III, IV, and V will follow the Simon’s 2-stage minimax design • Added that Arms IVa and Va will not follow the Simon’s two-stage minimax design • Clarified that the Biomarker Cohort (Ovarian Cancer) will not follow the Simon’s two-stage minimax design • Removed “5 arms” • Added “indications include” • Added Arms IVa and Va will enroll up to 25 evaluable subjects each with dose administration • Added Arms IVa, MSS-CRC, and Va, PaC, to Dose Expansion Phase 2a • Added Arms IVa and Va to Inclusion Criteria #5 • Add/Clarified OC to Inclusion Criteria #5 • Added patient specific criteria for Arms IVa and Va to Dose Expansion Phase • Added to Exclusion #2 that subjects with endocrine related AEs <2 that require treatment may be eligible • Updated Study Rationale to justify the basis for adding arms IVa and Va • Added Background • Replaced “Pembrolizumab IB” with “Investigator’s Brochure”

		• Replaced "pembrolizumab" with "MK-3475" • Deleted "and regardless or tumor type" • Added Arms IVa and Va throughout the protocol where applicable • Clarified text regarding the life of administration to "completion of 35 cycles of administration (approximately 2 years)" with NT-I7 and pembrolizumab • Updated "5.5 Biomarker Cohort" to "5.5 Subject Expansion" • Updated "5.5 Biomarker Cohort" to "5.6" • Updated the Study Schema • Added Arms IVa and Va to footnote 21 • Clarified in footnote 24 that Biomarker Cohort applies to NT-I7 increase to 1200 ug/kg on C5D1 • Added in footnote 24 that Arms IVa and Va apply to NT-I7 increase to 1200 ug/kg on C5D1 • Added to footnote 25 Arms IVa and Va • Added footnote 26 as option applicable to Arms IVa and Va • Moved "Dose re-escalation" to another section • Replaced PRA Health Sciences with ICON • Clarified ICON contact numbers • Deleted the requirement for a MRI brain scan with Arms I, II, and III at initial tumor imaging • Added that a MRI brain scan is preferred with Arms I, II, and III at initial tumor imaging • Clarified which arms will and will not have an interim analysis • Clarified which arms the DMC will conduct an interim analysis • Updated "1st tumor assessment" to "2nd tumor assessment" • Updated 150 subject to 210 subjects for phase 2a efficacy • Deleted "in each Phase 2a arm" • Added "Description analysis will be performed for Arms IVa and Va at the end of the enrollment" • Add "evaluable" 8 and 17 subjects when applicable • Added the missing word "protocol" to section 11 • Updated references Administrative Changes • Updated version number and date • Updated Table of Contents • Corrected typos, spelling and grammatical errors throughout • Administrative changes to dates, version numbers, and colors • Updated the title of sponsor signatory
6.0	17 Nov 2022	<u>Amendment #5 (Summary of Changes)</u> • Throughout: Minor grammatical corrections • Administrative: Updated date, version, and NIT signatory • Section 1.1 Synopsis and Section 4.1 Inclusion Criteria: Added language indicating that MMR-deficient subjects in Arms IV

		and IVa (CPI-naïve R/R MSS-CRC) specifically are not eligible for the study. • Section 1.1: Corrected numbering of Arms in Phase I (I, II, III, IV and V rather than I, II, III, V and V). • Sections 1.1, 2.3, 3, 4.1, 6.4, 13.1, 15.5: Removed "v." from RECIST v1.1, to align with how RECIST 1.1 is written in the appendix. • Sections 1.1 and 5.7: Updated Study Schema to clarify the dosing for Biomarker Cohort. • Sections 1.1 and 5.8: Updated Study Treatment figure to include C6D15 optional biopsy, pembrolizumab only arrows, and iRECIST language. • Section 2.4.1.2: Updated language to indicate that GX-I7-CA-003 study is complete. • Section 2.4.1.2.3: Added statement that NIT-104 has closed to further enrollment and updated the title, location, and study design of NIT-109. • Section 3: Added Biomarker Cohort to opening paragraph about study objectives. • Section 4, Subject Selection: Revised language to remove possibility of Sponsor approval of protocol waivers or exemptions for recruitment/enrollment criteria. • Section 4.5: Revised language to indicate that subject must adhere to contraception requirement from time of consent rather than the day of study medication. • Section 5.2: Updated to indicate that GX-I7-CA-003 study is complete. • Section 5.4: Defined the RP2D for dose expansion. • Section 6.1, Table 3: Added sections 5.4 and 5.6 to footnote for referencing dose levels. • Section 6.1.1: Corrected NT-I7 chemical formula. • Section 6.4: Divided and rearranged section into three subsections for clarity and readability. • Section 6.5 Study Treatment Beyond Progression: Revised iRECIST language for clarity. • Section 6.6 Duration of Follow-Up and End of Study: Added language including subjects who have completed all 35 cycles of treatment, included iRECIST, and revised 6 weeks to 9 weeks. • Section 7.1: Clarified language around confirmed PD and ICF. • Section 7.4 Schedule of Assessments: o Revised language for CT/MRI Tumor Evaluation by RECIST 1.1 and iRECIST o Moved merged cells for general imaging information to start at Cycle 4, including a mark for imaging at Cycle 2 Day 1 o In Footnote 16, added language indicating that patients do not need to undergo additional imaging if it is less than 4 weeks after the previous scan.

		○ Clarified language, including removing language about optional C6D15 biopsy from footnote 21, as it is also in footnote 24. Also, moved footnote 21 from general TCR-seq Analysis heading to C1D1. ○ In Footnote 26, changed V to Va ○ Added AE review at screening and revised footnote 9, linking section 11 ○ Added Footnote 27 to the C1D2 Adverse Events Review to clarify that this visit can be performed by telephone. ○ Separated Footnote 23 into two footnotes (23 for Safety Followup and newly created 28 for Survival Followup) to clarify that Survival Followup is by telephone only and performed every 90 days starting 90 days after Safety Followup Day 90, and added "outcome of any ongoing adverse events" to the rationale for the followup. Clarified that Safety Followup visits will be performed in the clinic only. ○ Separated Footnote 17 into two footnotes; 17 retained screening biopsy language and was moved from the Tumor Biopsy heading to the screening timepoint in the table. The remainder of the footnote became new footnote 29, which is attached to the Tumor Biopsy C2D8 timepoint in the table. Deleted the language about pre-treatment biopsies needing to be taken within 28 days of dosing. ○ Added C2D15±7days timepoint to align with language in footnotes 21 and 29 and clarified language in footnote 29 to change C2D22 to C3D1. • Section 9.1 Prohibited Medications/Treatment: Revised language to include attenuated vaccines and to add restriction out to 90 days following the last dose of study drug. • Section 11.4 Adverse Events of Special Interest in NT-I7: Revised language for clarity, to match language used in other NT-I7 protocols, removing reference to Hy's law for drug-induced liver injury. • Section 13.3 End of Treatment and Follow-Up Tumor Imaging: iRECIST is not optional in this study; removed language suggesting that it was dependent on investigator choice. Revised imaging schedule from every 12 weeks to 90 days (+/- 7 days). • Section 15.4 Data Monitoring Committee (DMC): Changed name from Data and Safety Monitoring Committee to Data Monitoring Committee and revised descriptive language about the committee purpose and procedures. • Appendix A: Deleted bullets about central imaging vendor, because this study does not use one.
7.0	26 Oct 2023	<u>Amendment #6 (Summary of Changes)</u> • Throughout: Minor corrections to grammar and formatting.

		• Administrative: Updated version and date • Section 1.1 Synopsis: Added inclusion criterion #9 indicating that an ECG with QTcF <470 ms is required and that pts with QTcF equal to or greater than 470 ms will require clearance by a local cardiologist. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. • Section 2.3 Study Rationale: Efficacy data for Arms IV and V was updated with data from the completed cohorts and references have been added. • Section 2.4.1.2.2 Completed Study GX-I7-CA-003: Table 1 has been deleted, as this information is available in the NT-I7 Investigator's Brochure. • Section 2.4.1.3 Benefit-Risk Conclusions: Have updated in accordance with NT-I7 IB v10. • Section 3, Objectives and Endpoints: Revised the method that will be used to identify tumor-infiltrating lymphocytes for compliance with Good Clinical Laboratory Practice (GCLP). • Section 4 Subject Selection: Added language stating that informed consent is considered to be withdrawn for patients who do not meet eligibility criteria after screening is completed ("screen failure"). • Section 4.1 Inclusion Criteria: Added inclusion criterion #9 indicating that an ECG with QTcF <470 ms is required and that pts with QTcF equal to or greater than 470 ms will require clearance by a local cardiologist. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. • Section 6.4.2 Subject Discontinuation/Withdrawal from Study: Added language indicating that a subject may be withdrawn from the study if they do not meet eligibility criteria ("screen failure"). • Section 6.4.2 Subject Discontinuation/Withdrawal from Study. Added an option for subjects to partially withdraw from active participation in the study and scheduled visits, but allow status followup via telephone or medical record review. • Section 7.1 Informed Consent: Added language to clarify that informed consent must be obtained prior to performing any study-specific procedures. • Section 7.4, Schedule of Assessments: o Removed prior and concomitant medications from Survival Follow-up to align with Footnote 4. o Added adverse events review to 90-day Safety Follow-up visit and revised Footnote 9 to indicate review of AEs and SAEs through 30-day safety follow-up and SAEs only from 30-days to 90-day safety follow-up visit.

		○ Revised 12-lead EKG row to add testing at C5D1 and Subsequent Cycles. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. ○ Added row for Cardiac Enzymes with testing at Screening, C1D1, C5D1, Subsequent Cycles, and End of Treatment. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. ○ Added rows for Echocardiogram and Cardiologist visit at Screening, C1D1, C5D1, Subsequent Cycles, and End of Treatment. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. ○ Revised Footnote 10 to incorporate guidance for serum cardiac enzyme testing and increase frequency of duplicate EKG to every 4 weeks. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. ○ Added Footnote 30 to include procedures for echocardiogram and cardiologist visit if ECG or serum cardiac enzyme levels are clinically significant. This change is in response to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. • Section 8.1 Dose Modification of NT-I7: Revised the guidance for myocarditis; rather than withholding until resolved at Grade 1, any grade of myocarditis will result in NT-I7 discontinuation. Additional precautions for myocarditis are included due to two fatal events in NIT-sponsored studies with NT-I7 in combination with checkpoint inhibitors. • Section 8.2 Dose Modification of Pembrolizumab: Updated information, including Tables 4 and 5, to match the guidance in the pembrolizumab IB v23. • Section 11.1 Adverse Events and Potential Risks List: Deleted section 11.1.1 and the associated table, and revised language to refer to the latest version of the NT-I7 IB for adverse events and potential risks. • Section 11.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information: Deleted mention of Events of Clinical Interest from the guidance about all AEs, as these are considered SAEs. • Section 11.3.2 Expedited Reporting Guidelines: Revised window of time for reporting a death via both expedited and routine reporting from 30 to 90 days after last administration of study agent. Revised classification of death due to PD to be

		"Grade 5 "Malignant neoplasm progression" under the system organ class (SOC) 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)'". • Section 11.6 Events of Clinical Interest (ECI) in Pembrolizumab: Removed "non-serious and serious" language, to clarify that ECIs must be reported as serious. • Section 11.8 Pregnancy: Revised reporting window for pregnancy from 120 days to 90 days after the last dose of study treatment, for consistency with section 11.3.1. • Section 14.1 Responsibility for Data Submission: Added language clarifying expectations surrounding data submission. • Section 14.3 Study Oversight: Added language clarifying expectations about conduct and cooperation with study oversight and access to study-related records, including a statement that protocol waivers will be prohibited. • Signature of Investigator page: Moved before Protocol Revisions to align with NIT protocol formatting.

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1. Protocol Summary

1.1. Synopsis

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
Study Phase	Phase 1b/2a
Clinical Indications	○ CPI treated R/R triple negative breast cancer (TNBC) ○ CPI treated R/R non-small cell lung cancer (NSCLC) ○ CPI treated R/R small cell lung cancer (SCLC) ○ CPI naïve R/R microsatellite stable colorectal cancer (MSS-CRC) ○ CPI naïve R/R pancreatic cancer (PC) ○ CPI naïve R/R ovarian cancer (OC) *CPI: Checkpoint inhibitors = anti-PD-1/anti-PD-L1* *R/R: Relapsed/Refractory*
Study Type	Phase 1b/2a, non-randomized, open-label study of NT-I7 in combination with pembrolizumab
Primary Objectives	<u>Phase 1b:</u> • To determine the safety and tolerability, including determination of the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of NT-I7 in combination with pembrolizumab in subjects with advanced solid tumors. <u>Phase 2a:</u> • 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 1.1 (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.

Secondary Objectives	Phase 1b/2a: • To further assess the anti-tumor activity of NT-I7 in combination with pembrolizumab in these patient populations based on 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 • To assess the anti-tumor activity of NT-I7 in combination with pembrolizumab in subjects with CPI-naïve R/R OC based on ORR, DoR, DCR, PFS, and OS by RECIST 1.1 and iRECIST. • To evaluate immunogenicity of NT-I7 administered in combination with pembrolizumab in these patient populations.
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, PC, and OC).
Study Design	This is a multicenter, open-label Phase 1b/2a study of NT-I7 in combination with pembrolizumab. The study consists of a dose escalation phase (Phase 1b) followed by a dose expansion phase (Phase 2a) and a Biomarker cohort. 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 dose levels 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 dose level). Doses may be de-escalated to one or two levels (e.g., 360 µg/kg

	or 240 µg/kg IM Q6W) depending on the pre-defined Dose-Limiting Toxicity (DLT) criteria. Pembrolizumab dose is fixed at 200 mg IV Q3W for all dose levels. Upon completion of Phase 1b, the MTD was not reached. There was 1 DLT (Grade 3 ALT increased) observed at the highest dose level 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, Arms I, II, III, IV, and V will follow the Simon's minimax two-stage design. Indications include 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 in Stage 2 for a total of 25 evaluable subjects per arm. Exact 95% binomial Clopper-Pearson confidence interval estimates of ORR from each arm is planned to support the primary hypothesis tests. Enrollment 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 (MSS-CRC) and Va (PC) will enroll up to 25 evaluable subjects respectively. NT-I7 will be administered at 1200 µg/kg IM Q6W. Pembrolizumab dose is fixed at 200 mg IV Q3W. The Biomarker Cohort will enroll up to 10 evaluable subjects with CPI-naïve R/R Ovarian Cancer (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. The treatment will be continued up to a maximum of 2 years or up to 35 cycles only. **Dose Escalation Phase (Phase 1b)** Phase 1b dose escalation for NT-I7 will follow the standard 3+3 design with three dose levels, and doses may be de-escalated to one or two levels (e.g., 360 µg/kg or 240 µg/kg IM Q6W) depending on the pre-defined Dose-Limiting Toxicity (DLT) criteria. Pembrolizumab dose is fixed at 200 mg IV

Q3W for this study.

Subjects are required to complete Cycle 1 to be considered evaluable for MTD determination unless discontinuation occurred due to a DLT (i.e., in the dose-determining set).

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 as described. In the event of unacceptable toxicity in the expansion phase, a lower dose will be explored.

Dose Expansion Phase (Phase 2a):

The selected arms in Phase 2a, arms I, II, III, IV, and V will follow the Simon's two-stage minimax design in each arm, and 5 arms are planned:

- 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 V : CPI-naïve R/R PC

In Stage 1 for arms I, II, III, IV, and V, up to 17 evaluable subjects will be enrolled and treated per arm. If at least one subject achieves objective response (complete response [CR] or partial response [PR]) 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.

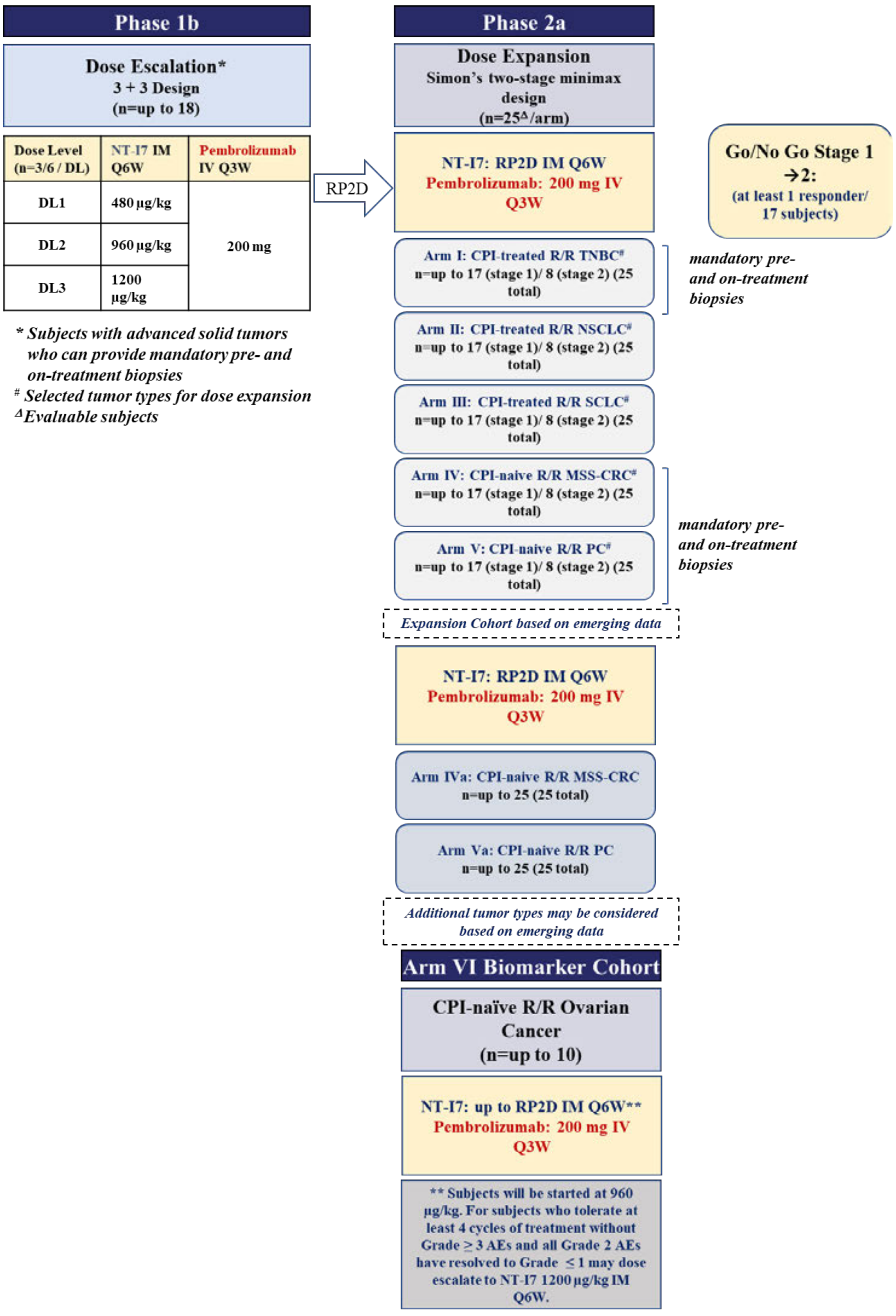
Arms IVa (MSS-CRC), Va (PC), and the Biomarker Cohort will not follow the Simon's two-state minimax design. Arms IVa and Va will enroll up to 25 evaluable subjects per arm. NT-I7 will be administered at 1200 ug/kg IM Q6W, with Pembrolizumab fixed dose at 200 mg IV Q3W.

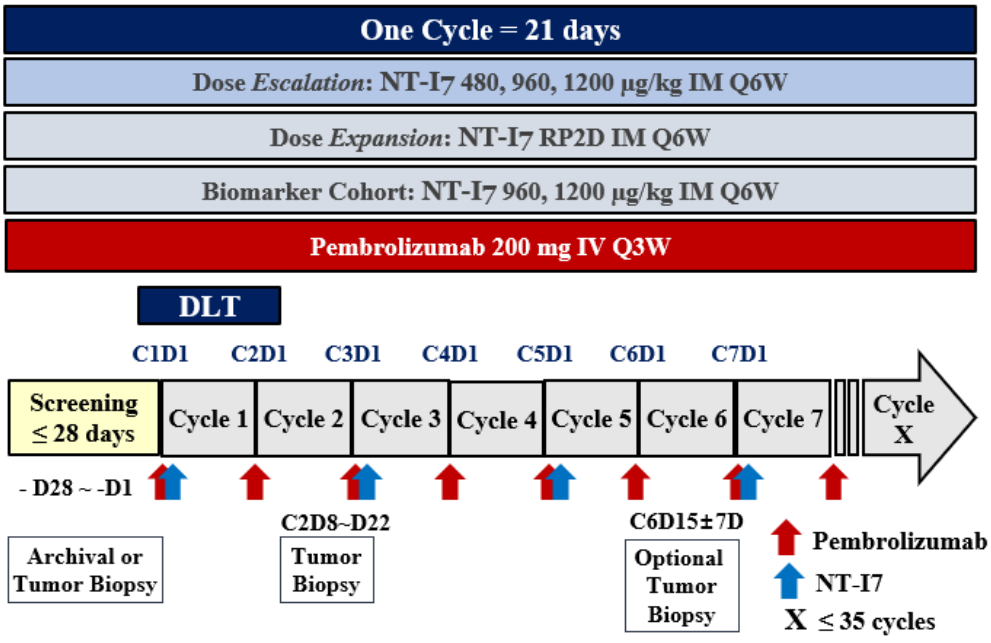
- Arm IVa : CPI-naïve R/R MSS-CRC
- Arm Va : CPI-naïve R/R PC

Biomarker Cohort:

The Biomarker Cohort is designed to assess the correlation between tumor infiltrating lymphocytes (TILs) and clinical benefits of NT-I7 in combination with pembrolizumab in subjects with CPI naïve R/R Ovarian Cancer (OC). Up to 10 evaluable subjects will be enrolled to obtain at least 4 pairs of evaluable

pre- and on-treatment tumor biopsies. The starting dose level of NT-I7 is planned at 960 µg/kg IM Q6W. Pembrolizumab dose is fixed at 200 mg IV Q3W for all dose levels. 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.



Treatment Schema	 **CT/MRI** **Radiological tumor assessments will be conducted every 2 cycles (6 weeks ±1 week) during the first 6 months, and every 3 cycles (9 weeks ±1 week) thereafter. Confirmatory scans must be performed at >4 weeks after initial assessment of response to confirm a best response of CR or PR, whenever disease progression is suspected (e.g., symptomatic deterioration), and at End of Treatment visit. If disease progression is identified by RECIST 1.1, a second scan will be scheduled 4-8 weeks later to confirm disease progression by iRECIST. (See Section 13 and Appendix A for details).** **Tumor Biopsy** **Pre-treatment biopsy/tissue collection (fresh) must be obtained within 28 days prior to Cycle 1, Day 1, unless archival tissue is available. On-treatment tumor biopsy must be obtained within 7 days of Cycle 2, Day 15 (i.e., between C2D8 and C2D22) and an optional tumor biopsy may be performed for the biomarker cohort or expansion cohorts IVa and Va on C6D15 ±7 days.**
Rationale for Dose Selection	Ongoing clinical study of NT-I7 monotherapy in patients with advanced solid tumors (Study GX-I7-CA-003) demonstrated an increase of ALC and multiple T-cell subsets in the peripheral blood in a dose-dependent manner until 720 µg/kg where the increases appeared to plateau. However, comparative tumor infiltrating lymphocytes (TIL) data in cancer patients is not yet available, although it is possible that higher TIL responses may be observed at doses higher than 720 µg/kg. Further, our preclinical data also suggested a dose-dependent increase in the peripheral ALC which appeared to plateau out at 2.5 mg/kg (i.e., no significant difference between 2.5 mg/kg and the higher dose of 10 mg/kg), but there were significantly more TILs, especially CD8+ T cells, at the 10 mg/kg dose. This animal dose of 10 mg/kg roughly translates to 810 µg/kg human dose. In addition, since 10 mg/kg was the highest dose tested in

	the animal model, it is not known whether higher doses would result in more TILs. Thus, both 960 µg/kg and 1200 µg/kg dose levels are selected for testing. The 480 µg/kg dose is chosen as the starting dose for NT-I7 based on the following rationales: 1) the safety profile of the combination, pembrolizumab + NT-I7, is not known; 2) based on the data from Study GX-I7-CA-003, 480 µg/kg dose did increase peripheral ALC and multiple subsets of T cells, thus can potentially provide benefit to the patients; 3) there are large differences between 480 µg/kg , 960 µg/kg and 1200 µg/kg doses that may allow detection of the differences in pharmacodynamic parameters (e.g. peripheral ALC and TILs) between the three dose levels. Hence, based on the preclinical and clinical data, 480, 960, and 1200 µg/kg are selected for testing in this study.
Eligibility Criteria	**Inclusion Criteria:** Subjects must meet <u>all</u> of the following criteria to be included in the study: 1. Must be ≥18 years on the day of signing informed consent. 2. Be willing and able to provide written informed consent/assent for the study. 3. Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors who have disease progression after treatment with all available therapies for metastatic disease that are known to confer clinical benefit, or are intolerant to treatment, or refuse standard treatment. 4. Have measurable disease per RECIST 1.1 as assessed by the enrolling physician. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 5. Subjects enrolling in the Phase 1b, Arms I, IV, IVa, V, and Va of the Phase 2a, and the Biomarker Cohort OC must have biopsiable disease (i.e., have at least 1 tumor lesion that is accessible and feasible for biopsy) as determined by the enrolling physician. Willing to provide archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue block is preferred to slide. Newly obtained biopsy is preferred to archived tissue. 6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. 7. Subjects must have a life expectancy of greater than or equal to 12 weeks per assessment from the enrolling physician. 8. Subjects must have adequate organ function as defined below: a. Absolute neutrophil count ≥1,500/µL b. Platelets ≥100,000/µL c. Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L (Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks)

d. Total bilirubin ≤1.5 × institutional upper limit of normal (ULN) OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
e. AST(SGOT)/ALT(SGPT) ≤2.5 × ULN (AST and/or ALT ≤5 × ULN for subjects with liver metastasis)
f. Alkaline phosphatase ≤2.5 × ULN (≤5 x ULN for subjects with documented liver involvement or bone metastases)
g. Creatinine ≤1.5 × ULN or Creatinine clearance (CrCl) ≥30 mL/min for subject with creatinine levels >1.5 x ULN. CrCl should be calculated per institutional standard
h. INR and aPTT ≤1.5 × ULN unless the subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

9. ECG demonstrating Fridericia's corrected QT interval (QTcF) < 470 ms. Patients with QTcF ≥ 470 ms will require clearance by a local cardiologist.
10. Female subjects who are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks; female subjects of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or to use dual methods of contraception for the duration of study treatment and for 120 days after the last dose of study treatment (pembrolizumab and/or NT-I7). Female subjects of childbearing potential (including women who have had a tubal ligation) must have a negative serum or urine pregnancy test within 72 hours prior to Cycle 1, Day 1. If the urine test is positive, or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Non-sterile male subjects who are sexually active with female partners of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or to use highly effective method(s) of contraception for the duration of study treatment and for 120 days after the last dose of study treatment (pembrolizumab and/or NT-I7).
12. And meet the requirements for the intended stages and arms (disease specific inclusion criteria), as following:

<u>Applicable to the Dose escalation phase (Phase 1b) only:</u>

a. Relapsed/refractory advanced solid tumors
   Note: *Prior anti-PD-1/anti-PD-L1 requires a 4-week washout period.*
b. Willing to provide pre- and on-treatment biopsies

<u>Applicable to the Dose expansion phase (Phase 2a) only:</u>

Anti-PD-1/anti-PD-L1 refractory criteria for CPI-treated TNBC, NSCLC, and SCLC

	Subjects must have progressed on treatment with an anti-PD-1/anti-PD-L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1/PD-L1 treatment progression is defined by meeting all of the following criteria: a. Has received at least 2 doses of an approved anti-PD-1/anti-PD-L1 mAb. ***Note:*** *Prior anti-PD-1/anti-PD-L1 requires a 4-week washout period.* b. Has demonstrated disease progression after anti-PD-1/anti-PD-L1 treatment as defined by RECIST 1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression. (1) ***Note:*** *This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.* c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/anti-PD-L1 mAb. **Specific to Arm I: CPI-treated R/R TNBC** a. Histopathologic or cytologic documented TNBC. Tumors must have been confirmed negative for ER and PR by IHC (<1% positive tumor nuclei, as per ASCO-CAP guideline recommendations) and negative for HER2 by IHC or fluorescent or chromogenic in situ hybridization (FISH or CISH). b. Received one or more prior therapies for TNBC in the advanced or metastatic setting, and prior treatment (for advanced, metastatic or (neo) adjuvant) must have included a taxane and/or anthracycline-based therapy and anti-PD-1/anti-PD-L1. c. Willing to provide pre- and on-treatment biopsies. **Specific to Arm II: CPI-treated R/R NSCLC** a. Had prior treatment with CPI. Subjects with EGFR, BRAF, or ROS1 mutations or ALK translocations are required to have received prior therapy with the appropriate TKI; prior platinum-based chemotherapy is not required for this specific patient population. **Specific to Arm III: CPI-treated R/R SCLC** a. Recurrent extensive-stage SCLC. b. Received prior CPI therapy. **Specific to Arm IV and IVa: CPI-naïve R/R MSS-CRC** a. MSS-CRC (categorized as MSS by immunohistochemistry (IHC) or polymerase chain reaction (PCR)-based local assay at any time prior to

screening or by the central laboratory). ***Note:*** *Subjects that are MMR deficient, microsatellite instability-high (MSI-H) or microsatellite unstable CRC are not eligible.*

b. Previously treated with standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan; subjects treated with CPI are not eligible.
c. Willing to provide pre- and on-treatment biopsies.

Specific to Arm V and Va: CPI-naïve R/R Pancreatic Cancer

a. Have documented radiographic progression to or documented intolerance of first line systemic chemotherapy which included either gemcitabine or Fluorouracil (5-FU)-based regimen (including capecitabine); subjects treated previously with CPI are not eligible.
b. Willing to provide pre- and on-treatment biopsies.

Specific to Biomarker Cohort: CPI-naïve R/R Ovarian Cancer

a. Up to 5 prior lines of treatment, including platinum-based treatment(s); subjects treated previously with CPIs are not eligible.
b. Willing to provide pre- and on-treatment tumor biopsies.

Exclusion Criteria

Subjects meeting <u>any</u> of the following criteria are not eligible for enrollment in the study:

1. Pregnant, lactating or breastfeeding or expecting to conceive or father children within the study duration from screening through 120 days after the last dose of study treatment.
2. Receiving chemotherapy or any anti-cancer therapy (approved or investigational) with half-life <1 week within 30 days or 5 half-lives, whichever is shorter, prior to first dose of study treatment. Receiving treatment with immune CPIs, immunomodulatory monoclonal antibodies (mAbs), and/or mAb-derived therapies within 4 weeks prior to first dose of study treatment.
   Note: *All AEs related to previous therapies, except alopecia, must be resolved to ≤Grade 1 or baseline. Subjects with Grade <u>≤</u>2 neuropathy may be eligible. Subjects with endocrine-related AEs Grade <u>≤</u>2 requiring treatment or hormone replacement may be eligible.*
3. Has received prior radiotherapy within 2 weeks of start of study treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week

	washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease. 4. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable (without evidence of progression by repeat imaging (during screening) for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using systemic steroids for CNS symptom management for at least 14 days prior to first dose of study treatment. 5. Subjects who have not recovered from AEs (other than alopecia, vitiligo, neuropathy or endocrinopathy managed with replacement therapy) due to prior agents administered (i.e., have residual toxicities >Grade 1). 6. Concurrent or previous other malignancy within 3 years of study entry, except cured basal or squamous cell skin cancer, transitional cell carcinoma of urothelial cancer, carcinoma in-situ of the breast or cervix. 7. History of severe hypersensitivity reactions to monoclonal antibodies (mAbs) or intravenous immunoglobulin preparations; any history of anaphylaxis; prior history of human anti-human antibody response; known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. ***Note:*** *Subjects with severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients are also excluded.* 8. Subjects who have spinal cord compression, not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to screening. 9. Subjects who have autoimmune disease history within the past 2 years, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barre syndrome, multiple sclerosis, vasculitis or glomerulonephritis. 10. Have active and clinically relevant bacterial, fungal, viral, or TB infection, including known Hepatitis A, B, or C or HIV (testing not required). 11. Clinically significant cardiac disease, including, but not limited to, any of the following: Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2); clinically significant and uncontrolled atrial fibrillation; history of acute coronary syndromes including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting < 6 months prior to screening; symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to

	screening except controlled atrial fibrillation and paroxysmal supraventricular tachycardia. 12. Subjects who have received treatment with systemic immunosuppressive medications (including, but not limited to, systemic prednisone >10 mg/day or its equivalent, cyclophosphamide, azathioprine, methotrexate, thalidomide and antitumor necrosis factor [anti-TNF] agents) within 7 days prior to first dose of study treatment. ***Note:*** *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.* 13. History of allergy or intolerance (unacceptable AEs) to study drug components or polysorbate-80-containing infusions. (***Note:*** *Polysorbate 80 is a buffer used to make NT-I7).* 14. Has a history of non-infectious pneumonitis that required steroids or current pneumonitis. 15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the enrolling physician. 16. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study. 17. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), 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. 18. Has had an allogenic tissue/solid organ transplant or bone marrow transplant. 19. 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, OX-40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE.
Number of Subjects	Up to 238 subjects are planned to be enrolled (up to 18 subjects in the Phase 1b, up to 210 subjects in the Phase 2a and up to 10 subjects in the Biomarker Cohort).
Power Calculations	This will provide an estimated 80% power per selected arms in the Phase 2a stage of the study for the primary hypothesis test using the Simon minimax design, for 4% vs 21% ORR, at 1-sided alpha = 0.025, as well as approximately 25 evaluable subjects per arms for 95% exact binomial Clopper-Pearson confidence intervals for ORR from the design (per arm). The design has futility interim analysis in each arm (based on ORR) at 17 evaluable subjects and

	maximum sample size of 25 evaluable subjects per arm. To account for non-evaluable subjects, it is planned to enroll up to 30 subjects per arm in Phase 2a.
Number of Clinical Sites	Approximately 8 study sites are planned to participate in this study
Duration of Participation	Each subject will participate in the study from the time the Informed Consent Form (ICF) is signed through final protocol-specific follow-up. The active study will end when the last subject completes the 90-day safety follow up visit, approximately 24 months after enrollment.
Estimated Duration of Study	Approximately 36 months after the last subject is enrolled.

2. Introduction

2.1. PD-1 Blockade and Solid Tumors

The immune system functions to protect the host immunity by a series of co-inhibitory and co-stimulatory receptors and their ligands, known as immune checkpoints (2, 3). Several evidence suggest that tumors exploit these mechanisms to escape anti-tumor immune responses and ultimately progress, disseminate, and metastasize (2, 4). Among the significant pathways, programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) axis play a vital role in the physiological immune homeostasis and putatively serve as a means through which cancer cells evade the immune system (5).

Conventional therapies usually target a particular molecule in the tumor cells, in which most tumor responses last until the cancer develops a way to bypass the blocked pathway, whereas PD-1/PD-L1 blockade releases negative regulators of immune checkpoints. In addition, numerous tumor types express high PD-L1 levels suggesting that PD-1/PD-L1 pathway activation is a common mechanism used by these tumors to avoid immune surveillance and to continue rapid growth. In many tumor types, high levels of PD-L1 expression correlate with better response to PD-1/PD-L1 inhibitors. Thus, development and application of immune CPIs that block PD-1/PD-L1 interaction result in very durable response and prolonged survival in patients. However, adverse events, low response rates and eventual progressions warrant for better understanding of PD-1/PD-L1 pathway to predict patient response and improve treatment efficacy and safety (6).

With the approval of pembrolizumab for the treatment of advanced melanoma in September 2014, to date, at least 500 clinical studies with PD-1 signal inhibitors have been conducted with nine types of antibodies from eight pharmaceutical companies on at least 20 types of solid and hematological malignant tumors 3 and the list is expanding. This basket study aims to study TNBC, NSCLC, SCLC, MSS-CRC, and PC where there are challenges, and room to improve current standards of immunotherapy.

2.1.1. Triple Negative Breast Cancer

Until October of 2018, phase 1 and 2 clinical studies evaluating PD-1 protein blockade as monotherapy in advanced TNBC showed disappointing response rates of 5 to 10% in unselected patient populations.

The approval of atezolizumab, a PD-L1 inhibitor, in advanced TNBC based on the Impassion 130 study has completely changed the field of immunotherapy in breast cancer (7). In this Phase 3 registration study, the median progression-free survival (PFS) in the intent-to-treat (ITT) population was significantly improved following the addition of atezolizumab as compared to nab-paclitaxel alone (7.2 vs. 5.5 months); further, among the PD-L1+ population, the respective PFS benefit was more pronounced (7.5 vs. 5.0 months). However, the current FDA approval of atezolizumab in the treatment of TNBC applies only to patients whose breast cancers express PD-L1.

In other studies, such as the Phase 1b KEYNOTE-012, pembrolizumab achieved an ORR of 18.5% in metastatic TNBC (8). It is worth noting that 15.6% patients were treatment-naïve at the time of metastatic disease in this study. In another Phase 2 KEYNOTE-086 study (cohort A), pembrolizumab led to an ORR and disease control rate of 5.3 and 7.6%, respectively, in pretreated TNBC patients (9). Preliminary data are available for the open-label Phase 1b/2 KEYNOTE-150 study assessing the combination of eribulin and pembrolizumab (10). Among 107 metastatic TNBC patients (106 evaluable for efficacy), 65 were CPI-naïve, while 41 had received one to two prior lines of therapy. Half of the patients in the study had PD-L1+ TNBC (45.8%). The ORR of the combination treatment in the overall population and that in the untreated and pretreated patients was 26.4, 29.2, and 22.0%, respectively.

In a Phase 3 KEYNOTE-119 trial evaluating pembrolizumab monotherapy compared to single-agent chemotherapy in previously treated metastatic TNBC, ORR were 9.5% vs 10.6% (ITT), 12.3% vs 9.4% (CPS ≥ 1), 17.7% vs 9.2% (CPS ≥ 10), and 26.3% vs 11.5% (CPS ≥ 20) (11).

Despite these practice-changing treatments in TNBC, there is significant room for improvement in the first-line treatment as well as treatment for patients who relapse after the initial response to CPIs.

2.1.2. Non-small Cell Lung Cancer

Pembrolizumab was approved in October 2015 for treatment of previously treated advanced or metastatic PD-L1-positive (at least 1%) NSCLC, based on the results of the randomized Phase 1b study KEYNOTE-001 (12).

Pembrolizumab was also approved for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (≥50%) with no EGFR or ALK genomic tumor aberrations based on the study of KEYNOTE-024 (13). The ORR was 44.8% in the pembrolizumab group and 27.8% in the chemotherapy group. In the Phase 3 KEYNOTE-042 study, subjects with previously untreated locally advanced or metastatic NSCLC without a sensitizing EGFR or ALK genomic tumor aberrations were given either pembrolizumab or chemotherapy. The ORRs were reported based on the PD-L1 expression in pembrolizumab vs chemotherapy patients; 39.1% vs 32.0% (TPS ≥ 50%), 33.2% vs 28.9% (TPS ≥ 20%), and 27.2% vs 26.5% (TPS ≥ 1%) (14).

In May 2017, pembrolizumab was approved in combination with pemetrexed and carboplatin for the first-line treatment of metastatic non-squamous NSCLC, irrespective of PD-L1 expression, based on the study of KEYNOTE-021 (15). In this Phase 2 open-label study, 55% patients in the pembrolizumab plus chemotherapy group achieved an objective response compared with 29% patients in the chemotherapy alone group.

In August 2018, FDA has approved an expanded label for pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations, based on results of the KEYNOTE-189 study (16). Median PFS was 8.8 months in the pembrolizumab-combination group and 4.9 months in the placebo-combination group.

Data from Phase 1 and Phase 3 studies of nivolumab and a Phase 2 study of atezolizumab—all in patients with previously treated NSCLC—provide further support for the durability of benefit with anti-PD-1 or anti-PD-L1 therapy in patients with NSCLC. Overall survival with nivolumab in the Phase 1 study was 18% after 3 years of follow-up and 16% after 5 years of follow-up. Similarly, in a pooled analysis after 3 years of follow-up in the Phase 3 CheckMate 017 and CheckMate 057 studies, an OS benefit was shown with nivolumab versus docetaxel. The 3-year survival for atezolizumab versus docetaxel in the Phase 2 POPLAR study was 18.7% versus 10.0%.

Although, immunotherapy is booming in the NSCLC space, tumor heterogeneity, mutational density, and the microenvironment play a vital role in the variability of responses and outcomes in immunotherapy-treated NSCLC patients regardless of the PD-L1 status (17). Further, there are challenges such as CPIs as monotherapy or in combination with chemotherapy only benefit a fraction of the patient population, primary resistance does exist and acquired resistance eventually develops.

2.1.3. Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for ~15% of all lung cancer and is the leading cause of cancer death among men and the second leading cause of cancer death among women worldwide (18). The prognosis of patients with SCLC is dismal with a 5-year survival rate of less than 5% and an average overall survival period of only 2–4 months for patients not receiving any active treatment (19).

Immunotherapy has been the most promising treatment with encouraging results. While nivolumab was the first FDA approved third-line drug for recurrent SCLC based on the Checkmate-032 study, atezolizumab + chemotherapy was the first Phase 3 (Impower 133) study that showed improved efficacy in the extensive stage SCLC in the first line setting (20).

Very recently, FDA granted accelerated approval of pembrolizumab in SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy based on the KEYNOTE-158 study (21). Importantly, studies such as KEYNOTE-028 (Phase 1b) and KEYNOTE-158 (Phase 2) have included patients with chemotherapy-refractory SCLC (≥3 lines of systemic therapy) treated with pembrolizumab. Of 83 evaluable patients obtained from the pooled data of KEYNOTE-028 (Phase 1b) and KEYNOTE-158 (Phase 2), ORR was 19.3%; 14 of 16 responders were PD-L1–positive.

In the ongoing Phase 1/2 CheckMate-032 study, patients received 3 mg/kg of nivolumab every 2 weeks, yielding an ORR of 11.9% regardless of PD-L1 expression. Among the responders, the median duration of response (DoR) was 17.9 months.

Checkmate 331 is a Phase 3 study of nivolumab or chemotherapy in relapsed SCLC after platinum-based first-line chemotherapy (22). At a follow-up of 15.8 months, no statistically significant improvement in OS was seen with nivolumab versus chemotherapy; median PFS was 1.4 months with nivolumab (1.4–1.5) and 3.8 months (3.0–4.2) with chemotherapy. Also, no differences were observed in terms of response rate (14% and 16%, respectively).

Despite immunotherapy having become a primary component of SCLC treatment, there are still many challenges, such as efficacy being very modest and limited to a small subset of patients.

2.1.4. Colorectal Cancer

In the colorectal arena, the first FDA-approved CPIs were pembrolizumab and nivolumab for the treatment of refractory deficient mismatch repair/microsatellite instability high (dMMR/MSI-H) metastatic CRC.

The notable success of these inhibitors in dMMR/MSI-H CRC has been attributed to the favorable immunogenic features of these tumors that contrast starkly with the "immune-cold" features of proficient mismatch repair/microsatellite stable (pMMR/MSS) CRC. It is estimated that dMMR CRC can yield about 20-times higher tumor mutational burden than pMMR, which is accountable for the higher TIL response and improved CPI efficacy (23).

It is perplexing that the objective response rate (ORR) was 0% (0 of 18) for patients with pMMR/MSS CRC as noted in the KEYNOTE-016 study (24). In this context, it is high time that combinatorial approaches are tested to sensitize the 'immunologically cold' MSS tumors. Specifically, strategies involving overcoming of the immunosuppressive tumor microenvironment, boosting effector T-cell function, increasing tumor antigenicity, and up-regulating diverse molecular mediators to elicit a more pro-inflammatory tumor milieu are of considerable interest.

2.1.5. Pancreatic Cancer

Several clinical studies in PC have shown that high PD-L1 expression relates to worse outcomes suggesting that blockade of PD-1/PD-L1 interaction may be effective in this tumor type (25-27) . However, data from 160 evaluable patients with advanced solid tumors in the Phase 1 anti-PD-L1, BMS-936559 (MDX1105) study showed no clinical response in PC patients.

In other two anti PD-1 studies, abominable results were achieved in PC cohorts. Specifically, in the KEYNOTE-001 study with pembrolizumab, out of the 30 patients, there was only one patient with pancreatic neuroendocrine tumor who achieved the best response as stable disease (SD) (28). Similarly, in a study of 7 patients with stage IV PC treated with nivolumab and dendritic cells, the best response achieved was partial response (2/7) (29).

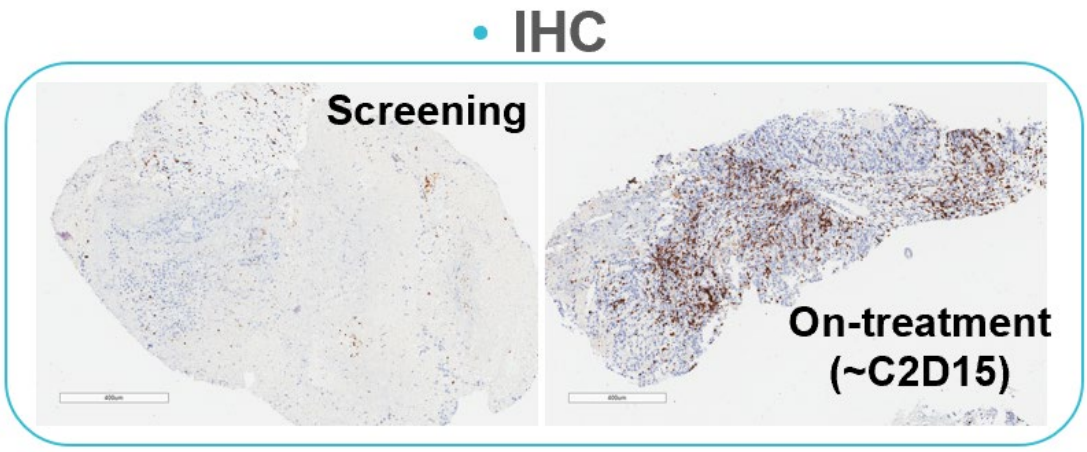
It is speculated that the efficacy of a single PD-1/PD-L1 blockade may be limited in PC for two primary reasons. First, immunosuppression caused by a high tumor burden is a reason why PC cannot respond to PD-1/PD-L1 blockade alone. Second, PC is intrinsically non-immunogenic (30). Thus, a combination strategy is the way of achieving specific anti-tumor responses in this aggressive tumor.

2.1.6. Ovarian Cancer

Ovarian Cancer (OC) is a potentially immunogenic tumor type that would likely benefit from immunotherapy since it has been shown that ovarian tumors with higher frequency of infiltrating lymphocytes are associated with better survival (31, 32) while higher PD-L1 expression at the tumor level is associated with poor prognosis (33). However, despite the high rate of tumor infiltrating lymphocytes (TILs), pembrolizumab monotherapy in patients with advanced recurrent

OC had limited efficacy with an ORR of 7.4-9.9% and a median PFS of 2.1 months ((34), NCT02674061), suggesting that blockade of the PD-1:PD-L1 axis is not sufficient to overcome the immunosuppressive tumor microenvironment (TME) in most OC patients. As a T-cell amplifier, NT-I7 has demonstrated its ability to expand T cells and promote tissue infiltration of lymphocytes in the TME of cancer patients. Thus, combination strategies including NT-I7 will likely increase the depth and breadth of the response to PD-1:PD-L1 blockade and thereby improve treatment efficacy.

In addition, preliminary data from the Dose Escalation phase (Phase 1b) of this study, NIT-110/KEYNOTE A60, showed significant increase of TILs in a subject with Clear Cell Ovarian Cancer.



Altogether, OC is well positioned to benefit from combination strategies that overcome the immunosuppressive TME. Including OC in this study potentially addresses a high unmet medical need for these patients. Furthermore, using OC as a model to determine the enhanced effects of pembrolizumab in combination with NT-I7 will provide relevant knowledge about pan-cancer biomarkers that may be used as predictors of anti-tumor activity.

Conclusion: Although immunotherapy has become new paradigm in cancer treatment, especially for tumors that are considered responsive to CPIs, the majority of patients fail to respond, and most responders eventually relapse. For tumors that are considered non-responsive to CPIs, such as MSS-CRC and PC, response to single-agent CPIs has been dismal. Thus, novel combinatorial strategies are needed to increase the depth and breadth of the response to CPIs.

2.2. Background

T-cells play a pivotal role in inducing antigen-specific immune responses to attack cancer cells, as they can recognize cancer antigens, destroy cancer cells and differentiate into memory T-cells to facilitate long term immunity. The anti-tumor efficacy of T-cells can be enhanced by increasing the diversity of the T-cell receptor repertoire to enable recognition of specific antigens

expressed by cancer cells, expanding T-cell clones responsive to tumor specific antigens and accelerating differentiation to memory T-cells to increase tumor tissue infiltration (35, 36).

It is well recognized that T-cell lymphopenia in cancer patients is associated with lower clinical anti-tumor responses and lower survival rates. To date, IL-2 (Proleukin® [aldesleukin]) is the only Food and Drug Administration (FDA)-approved cytokine product available as a therapeutic option to induce the proliferation and activation of T-cells. However, the clinical application of IL-2 is very limited due to serious adverse effects such as capillary leak syndrome and compromised efficacy through the increased proliferation of regulatory T-cells that inhibit anti-tumor immune responses (37, 38).

IL-7 is a crucial factor for the growth and activation of T-cells, and serves as a key player in the differentiation, proliferation and survival of naïve and memory T-cells. Importantly, it does not induce proliferation of regulatory T-cells. IL-7 is also a homeostatic cytokine, produced constitutively by a variety of stromal cells and by keratinocytes, dendritic cells, neurons, and endothelial cells but is not produced by lymphocytes. Its receptor (IL-7Rα) is expressed on resting T cells, and then rapidly down-regulated after T cell activation or IL-7 signalling. IL-7 is essential for T cell development in mice and humans, as well as for T cell homeostasis, because it is required to maintain naïve CD4+ and CD8+ T cells in vivo.

Recombinant human IL-7 (rhIL-7, CYT107) has been developed by Cytheris and tested in over 300 subjects including subjects with chronic HIV or HCV infections, subjects with refractory solid tumors, and subjects after allogeneic stem cell transplantation. In most studies, a marked increase in peripheral T cells and broadening of TCR diversity were seen to be dose-dependent, and rhIL-7 was well tolerated. The favorable safety profile of IL-7, in contrast to the severe toxicities of IL-2 (e.g., hematological toxicities, capillary leak syndrome), and its ability to reverse lymphopenia indicate that IL-7 is a promising therapeutic target that deserves further clinical investigation.

Although these combined clinical studies have demonstrated proof of mechanism in humans with regards to the safety, tolerability and substantial increases in T-cell count, rhIL-7 as atherapeutic previously faced numerous technical challenges including a short half-life of the drug, a lack of molecular stability of the intrinsically unstable protein, and the consequent poor production yield.

NT-I7 has the potential to provide immunocompromised subjects with a breakthrough solution by resolving issues with previous rhIL-7 candidates. As a fusion protein with the C-terminal of human IL-7 fused to hyFc long-acting platform, NT-I7 has overcome the fundamental problem of short half-life that stalled previous rhIL-7 programs. In non-clinical studies, NT-I7 increased peripheral T cells, anti-tumor efficacy, and tumor infiltrating lymphocytes, either as a monotherapy or in combination with chemo/radiotherapy and/or CPIs. In clinical studies, NT-I7 has demonstrated a well-tolerated safety profile and administration of NT-I7 led to a dose-dependent increase in the peripheral CD4+ and CD8+ T cells (naïve T cells, T_{EM}, T_{CM}, T_{EMRA}) and NK cells, but there was no dose-dependent increase in B cells.

2.3. Study Rationale

Cancer patients commonly suffer from lymphopenia, stemming either from their disease or therapeutic interventions, such as chemotherapy and/or radiotherapy. This cancer-associated lymphopenia correlates with decreased overall survival (39). IL-7 has been shown to increase TCR repertoire in subjects by (1) expanding naïve T cell pools (40) and (2) supporting subdominant T cell clones and improving the survival of the CD8 memory pool (41). In addition to reversing lymphopenia, IL-7 has also been shown to enhance the functionality of effector T cells (42) and to antagonize the immunosuppressive effects of Tregs and MDSCs (43). Based on these various mechanisms, IL-7 administration may significantly augment PD-1/PD-L1 blockade by virtue of increasing the number and effector function of tumor infiltrating lymphocytes.

Hence, based on the mechanism of action for NT-I7 and the data obtained from preclinical and clinical studies, adding NT-I7 to a PD-1 inhibitor, such as pembrolizumab, will potentially a) convert an immunologically "cold" tumor to a "hot" tumor; b) make a tumor that has developed resistance to a PD-1/PD-L1 inhibitor to become responsive again; and c) enhance the anti-tumor activity in immunologically "warm" tumors. In this clinical study, CPI treated R/R TNBC, NSCLC, and SCLC are selected to test the hypothesis of whether adding NT-I7 could convert these tumors which have developed resistance to a CPI to become responsive to a CPI again. CPI naïve MSS-CRC and PC are selected to test the hypothesis of whether adding NT-I7 could convert these immunologically "cold" tumors into "hot" tumors. In addition, CPI naïve OC is added to test whether NT-I7 could enhance the limited anti-tumor activity of single-agent CPI in these tumor types.

Emerging data from Arms IV and V in this trial have shown promising results, comparable to recently presented data from MSS-CRC subjects given pembrolizumab in combination with favezelimab, in which ORR was 6.3% (5/80) (44).

In the completed cohorts for Arms IV and V, ORR per iRECIST was observed in 11.1% of subjects in Arm IV (3/27 subjects) with 3.7% (1/27 evaluable) achieving confirmed PR per RECIST 1.1 (45), and in Arm V, ORR per iRECIST was achieved in 7.7% of subjects (2/26 evaluable) and RECIST 1.1 was achieved in 3.8% of subjects (1/26 evaluable) (46).

Previous studies in patients with CRC showed a positive relationship between tumor infiltration and good prognosis (47) (48). Similarly, CD8+ T cell infiltration in pancreatic cancer has been shown to improve sensitivity to anti-PD-1 therapy 46 (49). In the ongoing study, preliminary data suggests a possible role of NT-I7 in promoting tumor infiltration and increasing peripheral lymphocytes.

Based on these emerging data, we will add subjects in two new arms, Arms IVa and Va, anticipating that this addition will help establish a clinically significant ORR, elucidate NT-I7's mechanism of action in MSS-CRC and PC, and further propel the success of this trial.

2.4. Agents

2.4.1. NT-I7 (aka efineptakin alfa, rhIL-7-hyFc)

NT-I7 is a long-acting human IL-7 cytokine. It consists of human IL-7 fused to a hybrid Fc (hyFc) platform, which extends the half-life of NT-I7. HyFc is composed of the human IgD hinge region fused to the N-terminal region of CH2 from IgD, which is in turn fused to the C-terminal region of CH2 and the entire CH3 region of human IgG4. A detailed structural diagram of NT-I7 is shown in the *NT-I7 IB*.

2.4.1.1. Pre-clinical Studies

In preclinical studies, NT-I7 has demonstrated potent anti-tumor efficacy, both as a monotherapy and in combination with chemo/radiotherapy and immune checkpoint inhibitors (CPIs). By increasing peripheral and tumor infiltrating lymphocytes, and increasing T cell functionality, NT-I7 synergizes with therapies such as chemotherapy, radiation, and CPIs.

In a thymectomy-induced lymphopenia model (TILP) of C57BL/6 MC-38-bearing mice, a combination of NT-I7 and anti-PD-1 had significant anti-tumor effects that exceeded those of NT-I7 or anti-PD-1 therapies alone **(**Figure 1**).**

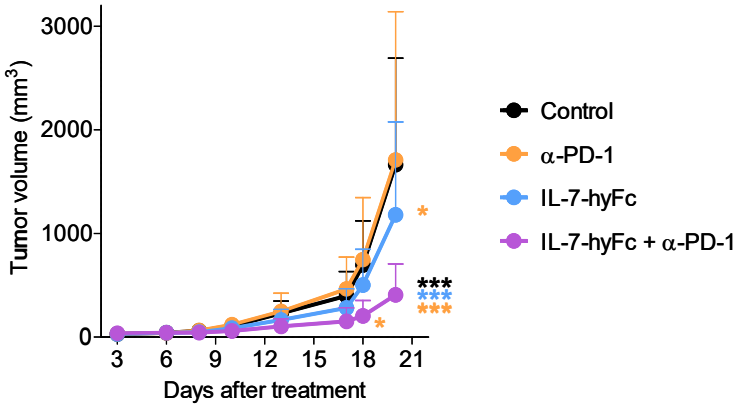


Figure 1: Synergistic anti-tumor efficacy of NT-I7 with anti-PD-1 on MC38 tumor model in sham and TILP hosts.

The combination treatment increased intratumoral CD4+ and CD8+ T cell infiltration compared to treatment with either agent alone (Figure 2). NT-I7 and anti-PD-1 combination therapy is further associated with a less exhausted phenotype of CD8+ TILs, where surface expression of co-inhibitory receptors PD-1 and TIM-3 was reduced on CD8+ TILs (Figure 3). A positive correlation between the number of CD8+ TILs and the suppression of tumor growth suggests that the combo therapy of NT-I7 with anti-PD-1 might increase tumor-specific cytotoxic CD8+ T cells.

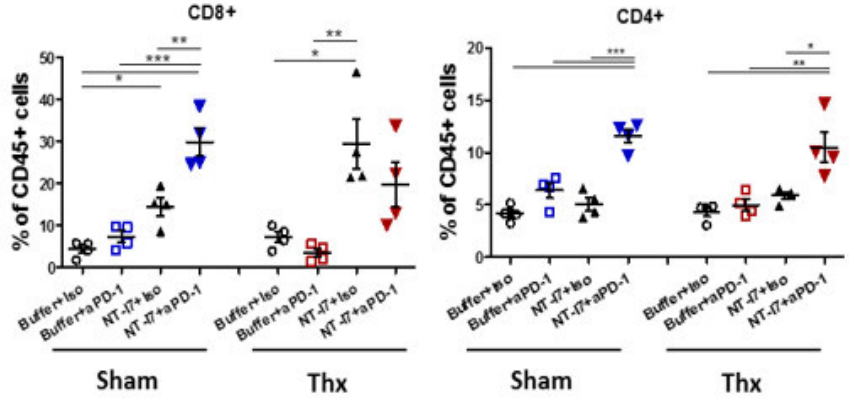


Figure 2: Synergistic anti-tumor efficacy of NT-I7 and anti-PD-1 combination therapy is associated with a greater increase in CD4+ and CD8+ T cell infiltration than in monotherapy.

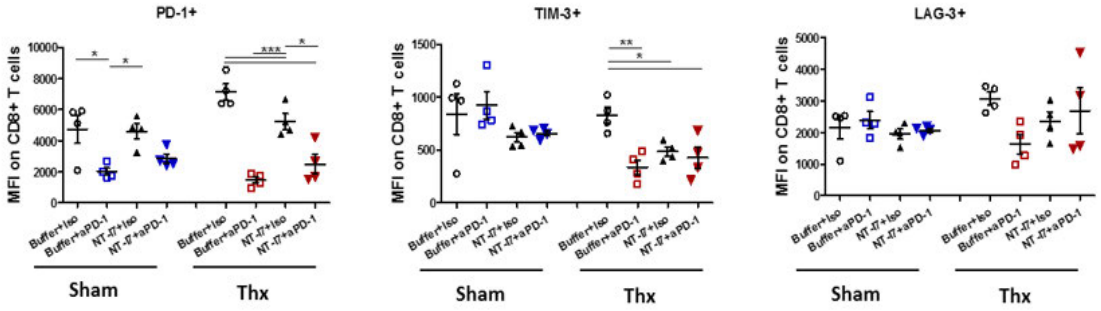


Figure 3: Down-regulation of PD-1 and TIM-3 immune checkpoint expression on CD8+ TILs is correlated with enhanced anti-tumor activity of NT-I7 and anti-PD-1 combination therapy.

A separate experiment evaluating 10mg/kg NT-I7 as a monotherapy in an MC-38 tumor model demonstrated that administration of NT-I7 created an immune-favorable tumor microenvironment (TME) by increasing the amount of tumor-infiltrating lymphocytes (TIL), the ratio of CD8+ Ts to regulatory Ts and MDSCs in the TME, and increasing the proliferative and effector capacity of CD8+ TIL (Figure 4).

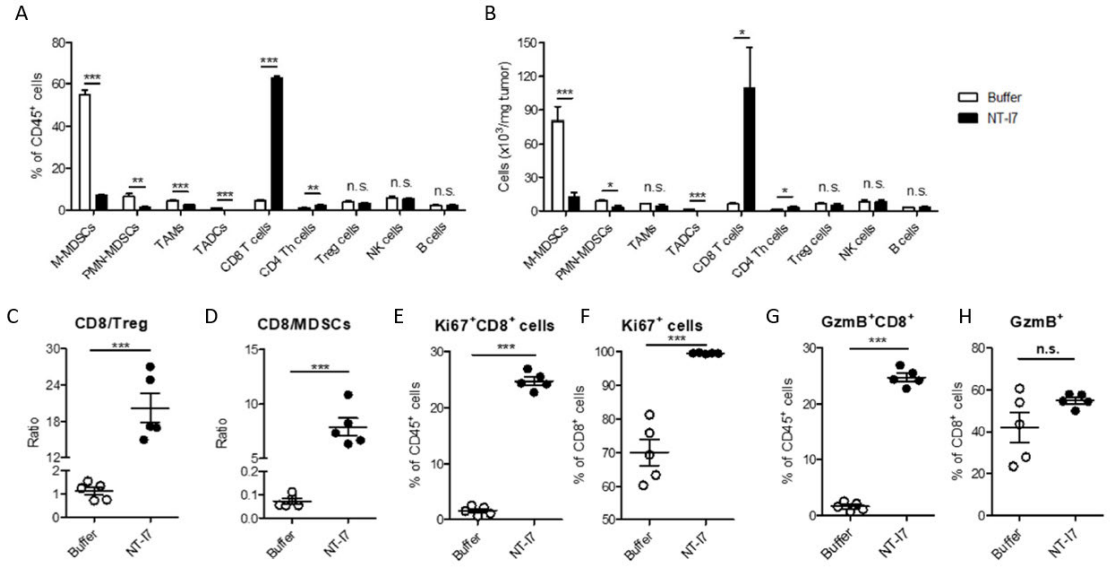


Figure 4: NT-I7 monotherapy promotes an immune-favorable tumor microenvironment (TME)

Thus, NT-I7 in combination with anti-PD-1 therapy can abrogate suppressive tumor milieu by inducing increased lymphocyte homing and TIL infiltration, and enhancing T cell functionality, thus lowering the barrier to sustained antitumor immunity.

2.4.1.2. Clinical Studies

Data from the completed studies of NT-I7 in healthy volunteers (GX-I7-HV-001) and patients with solid tumors (GX-I7-CA-003) showed that NT-I7 has been well tolerated with minimal toxicity and no treatment-related serious adverse events (SAEs). Increases in peripheral absolute lymphocyte count (ALC) and multiple subsets of CD4+ and CD8+ T cells have been observed following treatment (after an initial decrease likely due to homing to secondary lymphoid organs) with peak effect approximately 2 to 3 weeks after treatment. Exposure and pharmacodynamic effect were greater following intramuscular (IM) than subcutaneous (SC) administration.

2.4.1.2.1. Completed Study GX-I7-HV-001

GX-I7-HV-001 was a randomized, double-blind, placebo-controlled, dose-escalation, Phase 1 study to assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics after a single SC or IM administration of NT-I7 in healthy volunteers. Eligible subjects randomly received NT-I7 or placebo in an 8:2 ratio at one of the following doses: 20 µg/kg SC, 60 µg/kg SC, or 60 µg/kg IM.

NT-I7 was slowly absorbed, particularly after SC administration (time to maximum concentration [T_{max}]: 36 to 42 hours post dose) and was slowly removed from the body ($T_{1/2}$: 48 to 112 hours), resulting in a flat PK profile, typically seen in biologics. IM NT-I7 was more

rapidly absorbed than SC NT-I7 (median T_{max}: 4 hours vs 36 hours post dose for IM vs SC, respectively), and exposure was ~2 times larger following IM than SC administration at the same dose of 60 µg/kg, although the difference was not statistically significant. The PK parameters of NT-I7 were more variable after IM administration than SC injection. After SC administration, the exposure to IL-7 was increased in a dose-proportional manner. PK parameters are summarized in *NT-I7 IB*.

The pharmacodynamics assessments as observed by the ALC was increased in a dose-dependent manner after NT-I7 IM or SC administration (111.4% IM vs 75.1% SC for percent change from baseline at the same dose of 60 µg/kg). The increase in ALC peaked approximately 3 weeks after administration of NT-I7, and it lasted over several weeks. An initial 40% to 60% decrease in ALC was seen in all subjects within 4 days after NT-I7 administration was likely due to "homing effect". Pharmacodynamic parameters are summarized in *NT-I7 IB.*

Further, T-cell counts were also increased following treatment with NT-I7. Cell proliferation was observed for all CD4+ and CD8+ naïve T cells, effector memory T cells (T_{EM}), central memory T cells (T_{CM}), and terminally differentiated effector memory T cells (T_{EMRA}) at 168-hour post-dose (Day 7), and the most robust response was observed in NT-I7 60 µg/kg IM group.

NT-I7 was well tolerated in healthy volunteers after a single SC and IM administration at 20 to 60 µg/kg. A total of 58 treatment-emergent adverse events (TEAEs) were reported by 26 subjects (86.7%). No death or other SAEs were reported during the study. All TEAEs were resolved at follow-up. The majority of TEAEs were mild in intensity. Ten (33.3%) subjects experienced TEAEs of moderate intensity: injection site reaction (n=8 at 60 µg/kg SC; n=1 at 60 µg/kg IM), hepatic function abnormal (n=1 at 60 µg/kg SC). Injection site reactions were considered related to the study drug, while the relationship was unlikely for hepatic function abnormal. All other TEAEs were of mild intensity.

The incidence of subjects experiencing drug related TEAEs was similar in the active treatment cohorts. Drug-related TEAEs are summarized in *NT-I7 IB.*

All subjects had one or more out-of-range values for clinical laboratory tests, but none of these were considered clinically significant. No other clinically significant abnormalities were found in clinical laboratory tests, vital signs, 12-lead electrocardiogram, or physical examinations.

Most subjects (n=22, 91.7%) who received NT-I7 developed anti-drug antibody (ADA) during the study period, while there was no ADA detected in the placebo group. Neutralizing ADAs (NAbs) were observed in 41.6% (10/24) of the subjects 1 month after NT-I7 administration, and 45.8% (11/24) 2 months after NT-I7 administration, and 1 subject harbored neutralizing ADAs 5 months after NT-I7 administration. However, the presence of ADA and NAbs did not appear to affect drug exposure, safety profile, or pharmacodynamic parameters of NT-I7. For more information, refer to *NT-I7 IB.*

2.4.1.2.2. Completed Study GX-I7-CA-003

A Phase 1b trial of single-agent NT-I7 has been conducted in patients with advanced solid tumors in Korea (Study No. GX-I7-CA-003) utilizing a 3 + 3 dose escalation approach to determine the Recommended Phase 2 Dose (RP2D). The dose level ranges for this study include 60 µg/kg, 120 µg/kg, 240 µg/kg, 480 µg/kg, 720 µg/kg, 960 µg/kg, 1200 µg/kg, and 1700 µg/kg given intramuscularly (IM) every 3 weeks (q3w).

A total of 35 patients were enrolled and treated with NT-I7. There were 3 subjects who had AEs that resulted in death; none were considered related to NT-I7. Five subjects had 6 cases that were reported as SAEs. One of these SAEs was also a serious adverse drug reaction (ADR). The most common treatment-related AEs were injection site reactions, pyrexia, and abdominal pain. Dose-limiting toxicity (DLT) was reported in 1 of 2 subjects in the 1700 µg/kg dose group. The RP2D and maximum tolerated dose (MTD) were determined to be 1200 µg/kg.

PD data from the study showed ALC and naïve / less-differentiated memory subsets of CD4+ and CD8+ T cells increased in a dose-dependent manner after NT-I7 administration. The levels of endogenous IL-7 remained at normal levels without any significant change.

Pharmacokinetic data show that C_{max} and AUC last increased in a dose-proportional manner. The study confirmed that NT-I7 was safe and tolerated in patients with cancer, and that it can be safely administered without risk of cytokine storm when used in combination with other anticancer drugs. Safety data are summarized below.

A total of 225 TEAEs occurred in 35 subjects (100.0%). By dose group, 14 TEAEs were reported in the NT-I7 60 µg/kg group, 30 TEAEs in the NT-I7 120 µg/kg group, 15 TEAEs in the NT-I7 240 µg/kg group, 21 TEAEs in the NT-I7 480 µg/kg group, 35 TEAEs in the NT-I7 720 µg/kg group, 6 TEAEs in the NT-I7 960 µg/kg group, 88 TEAEs in the NT-I7 1200 µg/kg group, and 16 TEAEs in the 1700 µg/kg group. When the severity of AEs was graded using the NCI-CTCAE (Version 4.0), 118 TEAEs were mild (Grade 1), 84 TEAEs were moderate (Grade 2), 16 TEAEs were severe (Grade 3), and 4 TEAEs were life-threatening or required urgent intervention (Grade 4). Three TEAEs were reported as death related to AEs (Grade 5).
By preferred term (PT), the most common AEs were injection site reactions (61 TEAEs in 25 subjects [71.4%]), pyrexia (26 TEAEs in 15 subjects [42.9%]), and abdominal pain (10 TEAEs in 10 subjects [28.6%]).

There were 6 SAEs in 5 subjects (14.29%): 1 subject in the 120 µg/kg group had Grade 5 mesenteric arterial occlusion (not related to NT-I7); 1 subject in the 480 µg/kg group had Grade 3 ascites and Grade 5 upper gastrointestinal hemorrhage (both not related); 1 subject in the 1200 µg/kg group had Grade 2 azotemia and Grade 5 dyspnea (both not related); and 1 subject in the 1700 µg/kg group had Grade 3 hypersensitivity (related). The last event was also a serious ADR.

There were 10 AEs of special interest (AESI) as specified in the protocol in 5 subjects. The AESI included cases of potential drug-induced liver injury, conditions suggestive of autoimmune disorders, Grade 2 or higher AEs suggestive of hypersensitivity or immune-mediated reaction, Grade 2 or higher hypoxia or dyspnea, and Grade 2 or higher pleural effusion. One AESI

(pneumonia) occurred in 2 subjects, all others were reported for a single subject (anaphylactic reaction, hypersensitivity, mesenteric arterial occlusion, pyrexia, hepatic failure, pleural effusion, urticaria, and hypotension).

One of 2 subjects at 1700 µg/kg experienced DLT (hypersensitivity) as specified in the protocol. The RP2D and MTD of NT-I7 was determined to be 1200 µg/kg.

Clinically significant changes in plasma and serum chemistry results after the administration of study drug were reported as AEs or were judged to be due to progression of the underlying disease.

2.4.1.2.3. Other Studies

ABTC-1403 (also known as NIT-104) is an ongoing Phase 1 dose-escalation and pilot study of the effect of NT-I7 on CD4 cell counts in subjects with high grade gliomas and severe treatment-related CD4 lymphopenia after concurrent radiation therapy (RT) and treatment with temozolomide (TMZ). The NIT-104 study is closed to further enrollment. More details are provided in the *NT-I7 IB*.

NIT-106 is a Phase 1b/2a, open-label study to evaluate anti-tumor efficacy and safety of NT-I7 in combination with anti-PD-L1 (atezolizumab) in subjects with anti-PD-1/PD-L1 naïve or relapsed/refractory high-risk skin cancers. The study is ongoing in the US.

NIT-109 is an open-label, randomized, A Multicenter, Open-label, Phase 2 Study of NT-I7 in Combination with Nivolumab in Subjects with Relapsed/Refractory Gastric or Gastro-Esophageal Junction or Esophageal Adenocarcinoma who Progressed on or Intolerant to 2 or more Prior Lines of Systemic Therapy. The study is ongoing in the US and Poland.

No efficacy data are available for any of the studies up to date.

2.4.1.3. Benefits and Risks Conclusions

Safety, pharmacodynamic, and PK data for NT-I7 are available from one completed study in healthy volunteers, four completed studies in cancer patients, and 11 ongoing studies in patients with cancer and COVID-19. Based on these limited data, it can be concluded that:

- NT-I7 was well tolerated in healthy volunteers and adult subjects with cancer

- NT-I7 was generally well tolerated in combination with CPI in adult patients with relapsed/refractory (R/R) solid tumors. Myocarditis has been added as a potential risk for NT-I7 due to two fatal events when combined with pembrolizumab and atezolizumab, respectively. Myocarditis has an established association with both CPIs, and both patients had pre-existing cardiac risk factors; these may be more likely contributors to the events, but a causal relationship with NT-I7 cannot be ruled out.

- NT-I7 was slowly absorbed and eliminated, resulting in a flat PK profile, regardless of route of administration

- IM administration of NT-I7 resulted in more rapid absorption and had higher exposure to NT-I7 than did SC administration

- NT-I7 led to a dose-dependent increase in CD4+ and CD8+ T cells (naïve T cells, T_{EM}, T_{CM}, T_{EMRA}) and NK cells, but there was no dose-dependent increase in B cells

- IM administration of NT-I7 resulted in a more pronounced increase in lymphocytes over SC administration

The anti-tumor activity observed with NT-I7 as monotherapy or in combination with other anti-cancer agents, the well-tolerated safety profile seen in humans and the unique ability of NT-I7 to increase lymphocyte counts support further clinical investigation in patients with lymphopenia, including subjects with cancer who are often lymphopenic due to either the underlying diseases or prior anti-cancer treatments.

Based on the evaluation of the cumulative safety data available and the anticipated efficacy/ benefit information for NT-I7, the benefit-risk balance for the product remains favorable.

2.4.2. Pembrolizumab Background

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 subjects across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

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

2.4.2.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (50). 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 (51, 52).

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) (53, 54).

The structure of murine PD-1 has been resolved (55). 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 (54, 56-58). 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 (59, 60). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in TNBC, NSCLC, SCLC, MSS-CRC, PC, and OC.

2.4.2.1.1. Pre-clinical Studies

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 (61-67). 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 (25, 64, 66-68). 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* (66) 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).

2.4.2.1.2. Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5-to-7.5-fold exposure range (refer to the IB)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologic-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

3. Objectives and Endpoints

This is a multicenter, open-label Phase 1b/2a study to determine the MTD and/or RP2D, to assess the safety, and tolerability 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), and to assess a potential correlation between tumor infiltrating lymphocytes (TILs) and clinical benefits in subjects with CPI-naïve R/R OC. Specific objectives and corresponding endpoints for the study are outlined in the following Table 1.

Table 1: Objectives and endpoints

Objectives	**Corresponding Endpoints**
Primary Objectives	
Phase 1b: • To determine the safety and tolerability, including determination of the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of NT-I7 in combination with pembrolizumab in subjects with advanced solid tumors.	• Incidence, nature, and severity of adverse events graded according to NCI CTCAE v5.0. • Incidence and nature of DLTs. • Potential correlation of dose levels with safety and efficacy parameters.
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) per Response Evaluation Criteria in Solid Tumors by RECIST 1.1 and iRECIST	• Objective Response Rate (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: • To assess a potential correlation between tumor infiltrating lymphocytes (TILs) and clinical benefits in subjects with CPI-naïve R/R OC.	• Number, distribution, and phenotype of tumor-infiltrating lymphocytes (TILs). CD8+ TILs in tumor biopsy samples will be identified using a validated IHC assay and properly certified by a pathologist.
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.	• Objective Response Rate (ORR, Biomarker Cohort only) defined as the percentage of subjects who have at least one confirmed partial response (PR) or complete response (CR), per by RECIST 1.1 and iRECIST as determined by the investigator. • Duration of response (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. DoR will be assessed statistically via Kaplan-Meier methods and presented descriptively for the responders. Comparative assessments are not planned on this endpoint. • Disease Control Rate (DCR) for each individual arm, defined as proportion of subjects with a best overall response of CR, PR or SD, per RECIST 1.1 and iRECIST as determined by the investigator. DCR will be assessed statistically *via* Fisher Exact tests supported by Clopper-Pearson confidence intervals; all analyses will be interpreted descriptively. Comparative assessments are not planned on this endpoint. • Progression Free Survival (PFS) for each individual arm, defined as the time from the first study treatment (Cycle 1, Day 1) to the first occurrence of progression or

	death from any cause, whichever occurs first, per RECIST 1.1 and iRECIST as determined by the investigator. PFS will be assessed statistically via Kaplan-Meier methods and presented descriptively for all treated subjects in each study arm; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively. Comparative assessments are not planned on this endpoint. • Overall survival (OS) for each individual arm, defined as the time from first study treatment (Cycle 1, Day 1) to death from any cause. OS will be assessed statistically similarly to PFS (above).
Phase 1b/2a/Biomarker Cohort: • To evaluate immunogenicity of NT-I7 administered in combination with pembrolizumab in these patient populations.	• Incidence of anti-drug antibody (ADA) to NT-I7 during the study 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). All immunogenicity assays have been analytically validated.
Biomarker Cohort: • To assess the safety of NT-I7 in combination with pembrolizumab in subjects with CPI-naïve R/R OC	• Incidence, nature, and severity of adverse events graded according to NCI CTCAE v5.0.

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.	• 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 (Cmax), minimum serum concentration (Cmin), and clearance (CL). ELISA-based assay to measure serum NT-I7 levels has been analytically validated. In phase 1b and in the Biomarker Cohort, longitudinal samples will be collected from each subject to obtain a detailed PK profile. In phase 2a, a sparse sampling schema will be employed for population PK assessment. Individual PK measurements will be tabulated by arms along with descriptive statistics. Non-compartmental PK data analysis will be performed from each arm with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental PK parameters will be provided and may include area under concentration-time curve, maximum observed concentration (C_{max}), time to reach C_{max}, clearance, volume of distribution, and terminal half-life.
Phase 1b/2a/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,	• Number, distribution, and phenotype of tumor-infiltrating lymphocytes (TILs) (Biomarker Cohort to follow primary objective). TILs in tumor biopsy samples will be identified using a multi-spectral IF assay. Markers include, but are not limited to,

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-CRCand PC).	tCD3, CD8, Ki67, panCK, and nuclear stain. Image analysis will be performed using Halo Indica software. Descriptive statistics will be used to describe arm specific changes. • PD-L1 expression. PD-L1 expression will be performed using a 22C3 IHC assay in the tumor biopsy. PD-L1 mRNA expression by RNA sequencing analysis may also be explored. Descriptive statistics will be used to describe arm specific changes. • Expression of interferon γ (IFN-γ) and associated inflammatory gene expression in the tumor microenvironment. Based on tissue availability, gene expression analysis may be performed on tumor biopsy tissue sections. • Changes in tumor microenvironment 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 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, TCR repertoire diversity analysis by TCRseq, and immunostaining techniques such as multi-spectral 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

4. Subject Selection

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet entry criteria. Informed consent is withdrawn for patients who do not meet the eligibility criteria after screening is completed ("screen failure").

4.1. Inclusion Criteria

Subjects must meet all the following criteria for study entry:

1. Must be ≥18 years on the day of signing informed consent.
2. Be willing and able to provide written informed consent/assent for the study.
3. Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors who have disease progression after treatment with all available therapies for metastatic disease that are known to confer clinical benefit, or are intolerant to treatment, or refuse standard treatment.
4. Have measurable disease per RECIST 1.1 as assessed by the enrolling physician. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
5. Subjects enrolling in the Phase 1b and Arms I, IV, IVa, V, and Va of the Phase 2a, and the Biomarker Cohort must have biopsiable disease (i.e., have at least 1 tumor lesion that is accessible and feasible for biopsy) as determined by the enrolling physician. Willing to provide archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue block is preferred to slide. Newly obtained biopsy is preferred to archived tissue.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
7. Subjects must have a life expectancy of greater than or equal to 12 weeks per assessment from the enrolling physician.
8. Subjects must have adequate organ function as defined below:
   a. Absolute neutrophil count ≥1,500/µL
   b. Platelets ≥100,000/µL
   c. Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L (Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks)
   d. Total bilirubin ≤1.5 × institutional upper limit of normal (ULN) OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
   e. AST(SGOT)/ALT(SGPT) ≤2.5 × ULN (AST and/or ALT ≤5 × ULN for subjects with liver metastasis)
   f. Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN for subjects with documented liver involvement or bone metastases)
   g. Creatinine ≤1.5 × ULN or Creatinine clearance (CrCl) ≥30 mL/min for subjects with creatinine levels >1.5 × ULN. CrCl should be calculated per institutional standard.
   h. INR and aPTT ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
9. ECG demonstrating Fridericia's corrected QT interval (QTcF) < 470 ms. Patients with QTcF ≥ 470 ms will require clearance by a local cardiologist.

10. Female subjects who are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks; female subjects of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or to use dual methods of contraception for the duration of study treatment and for 120 days after the last dose of study treatment (pembrolizumab and/or NT-I7). Female subjects of childbearing potential (including women who have had a tubal ligation) must have a negative serum or urine pregnancy test within 72 hours prior to Cycle 1, Day 1. If the urine test is positive, or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Non-sterile male subjects who are sexually active with female partners of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or to use highly effective method(s) of contraception for the duration of study treatment and for 120 days after the last dose of study treatment (pembrolizumab and/or NT-I7).
12. Meet the requirements for the intended stages and arms (disease specific inclusion criteria), as follows:

Applicable to the Dose escalation phase (Phase 1b) only:

a. Relapsed/refractory advanced solid tumors
   Note: *Prior anti-PD-1/anti-PD-L1 requires a 4-week washout period.*
b. Willing to provide pre- and on-treatment biopsies

Applicable to the Dose expansion phase (Phase 2a) only:

Anti-PD-1/anti-PD-L1 refractory criteria for CPI-treated TNBC, NSCLC, and SCLC

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

a. Has received at least 2 doses of an approved anti-PD-1/anti-PD-L1 mAb.
   Note: *Prior anti-PD-1/anti-PD-L1 requires a 4-week washout period.*
b. Has demonstrated disease progression after anti-PD-1/anti-PD-L1 treatment as defined by RECIST 1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.(1)
   Note: *This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.*
c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/anti-PD-L1 mAb.

Specific to Arm I: CPI-treated R/R TNBC

a. Histopathologic or cytologic documented TNBC. Tumors must have been confirmed negative for ER and PR by IHC (<1% positive tumor nuclei, as per ASCO-CAP guideline recommendations) and negative for HER2 by IHC or fluorescent or chromogenic in situ

hybridization (FISH or CISH).

b. Received one or more prior therapies for TNBC in the advanced or metastatic setting, and prior treatment (for advanced, metastatic or (neo) adjuvant) must have included a taxane and/or anthracycline-based therapy and anti-PD-1/anti-PD-L1.
c. Willing to provide pre- and on-treatment biopsies.

Specific to Arm II: CPI-treated R/R NSCLC

a. Had prior treatment with CPI. Subjects with EGFR, BRAF, or ROS1 mutations or ALK translocations are required to have received prior therapy with the appropriate TKI; prior platinum-based chemotherapy is not required for this specific patient population.

Specific to Arm III: CPI-treated R/R SCLC

a. Recurrent extensive-stage SCLC.
b. Received prior CPI therapy.

Specific to Arm IV and IVa: CPI-naïve R/R MSS-CRC

a. MSS-CRC (categorized as MSS by immunohistochemistry (IHC) or polymerase chain reaction (PCR)-based local assay at any time prior to screening or by a central laboratory). ***Note:*** *Subjects that are MMR deficient or microsatellite instability-high (MSI-H) or microsatellite unstable CRC are not eligible.*
b. Previously treated with standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan; subjects treated with CPI are not eligible.
c. Willing to provide pre- and on-treatment biopsies.

Specific to Arm V and Va: CPI-naïve R/R Pancreatic Cancer

a. Have documented radiographic progression to or documented intolerance of first line systemic chemotherapy which included either gemcitabine or Fluorouracil (5-FU) based regimen (including capecitabine); subjects treated previously with CPI are not eligible.
b. Willing to provide pre- and on-treatment biopsies.

Applicable to Biomarker Cohort only:

a. **Specific to CPI-naïve R/R Ovarian Cancer** Up to 5 prior lines of treatment, including platinum-based treatment(s); subjects treated previously with CPI are not eligible.
b. Willing to provide pre- and on-treatment tumor biopsies.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment in the study:

1. Pregnant, lactating or breastfeeding or expecting to conceive or father children within the study duration from screening through 120 days after the last dose of study treatment.
2. Receiving chemotherapy or any anti-cancer therapy with half-life <1 week within 30 days or 5 half-lives, whichever is shorter, prior to first dose of study treatment. Receiving treatment with immune CPIs, immunomodulatory monoclonal antibodies (mAbs), and/or mAb-derived therapies within 4 weeks prior to first dose of study treatment. ***Note:*** *All AEs related to previous therapies, except alopecia, must be resolved to ≤Grade 1 or baseline. Subjects with ≤Grade 2 neuropathy may be eligible. Subjects with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.*
3. Has received prior radiotherapy within 2 weeks of start of study treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
4. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable (without evidence of progression by repeat imaging (during screening) for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using systemic steroids for CNS symptom management for at least 14 days prior to first dose of study treatment.
5. Subjects who have not recovered from AEs (other than alopecia, vitiligo, neuropathy or endocrinopathy managed with replacement therapy) due to agents administered more than 4 weeks earlier (i.e., have residual toxicities >Grade 1).
6. Concurrent or previous other malignancy within 3 years of study entry, except cured basal or squamous cell skin cancer, transitional cell carcinoma of urothelial cancer, carcinoma in-situ of the breast or cervix.
7. History of severe hypersensitivity reactions to monoclonal antibodies (mAbs) or intravenous immunoglobulin preparations; any history of anaphylaxis; prior history of human anti-human antibody response; known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
   Note: *Subjects with severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients are also excluded.*
8. Subjects who have spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to screening.
9. Subjects who have autoimmune disease history for the past 2 years, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barre syndrome, multiple sclerosis, vasculitis or glomerulonephritis.
10. Have active and clinically relevant bacterial, fungal, viral, or TB infection, including known Hepatitis A, B, or C or HIV (testing not required).
11. Clinically significant cardiac disease, including, but not limited to, any of the following: Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2); clinically significant and uncontrolled atrial fibrillation; history of acute coronary

syndromes including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting < 6 months prior to screening; symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to screening except controlled atrial fibrillation and paroxysmal supraventricular tachycardia.

12. Subjects who have received treatment with systemic immunosuppressive medications (including, but not limited to, systemic prednisone >10 mg/day or its equivalent, cyclophosphamide, azathioprine, methotrexate, thalidomide and antitumor necrosis factor [anti-TNF] agents) within 7 days prior to first dose of study treatment.
    Note: *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.*
13. History of allergy or intolerance (unacceptable AEs) to study drug components or polysorbate-80-containing infusions.
    Note: *Polysorbate 80 is a buffer used to make NT-I7.*
14. Has a history of non-infectious pneumonitis that required steroids or current pneumonitis.
15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the enrolling physician.
16. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.
17. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), 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.
18. Has had an allogenic tissue/solid organ transplant or bone marrow transplant.
19. 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, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE.

4.3. Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this study.

4.4. Meals and Dietary Restrictions

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

4.5. Contraception

NT-I7 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if NT-I7 or pembrolizumab has transient adverse effects on the composition of sperm.

Subjects 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, subjects of childbearing potential must adhere to the contraception requirement from time of consent (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 treatment.

If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5. Study Design

5.1. 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.

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 dose levels 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 dose level). Doses may be de-escalated to one or two levels (e.g., 360 or 240 µg/kg IM Q6W) depending on the pre-defined Dose-Limiting Toxicity (DLT) criteria. Pembrolizumab dose is fixed at 200 mg IV Q3W for all dose levels. Upon completion of Phase 1b, the MTD was not reached. There was 1 DLT (Grade 3 ALT increased) observed at the highest dose level 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 in Stage 2 for a total of 25 evaluable subjects per arm. Exact 95% binomial Clopper-Pearson confidence interval 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 Ovarian Cancer (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. Completion of 35 cycles of administration (approximately 2 years) with pembrolizumab and NT-I7.

5.2. Rationale for Dose Selection

Completed clinical study of NT-I7 monotherapy in patients with advanced solid tumors (Study GX-I7-CA-003) demonstrated an increase of ALC and multiple T-cell subsets in the peripheral blood in a dose-dependent manner until 720 µg/kg where the increases appeared to plateau. However, comparative tumor infiltrating lymphocytes (TIL) data in cancer patients is not yet available, although it is possible that higher TIL responses may be observed at doses higher than 720 µg/kg. Further, our preclinical data also suggested a dose-dependent increase in the peripheral ALC which appeared to plateau out at 2.5 mg/kg (i.e., no significant difference between 2.5 mg/kg and the higher dose of 10 mg/kg), but there were significantly more TILs, especially CD8+ T cells, at the 10 mg/kg dose. This animal dose of 10 mg/kg roughly translates to 810 µg/kg human dose. In addition, since 10 mg/kg was the highest dose tested in the animal model, it is not known whether higher doses would result in more TILs. Thus, both 960 µg/kg and 1200 µg/kg dose levels are selected for testing.

The 480 µg/kg dose is chosen as the starting dose for NT-I7 based on the following rationales: 1) the safety profile of the combination, pembrolizumab + NT-I7, is not known; 2) based on the data from Study GX-I7-CA-003, 480 µg/kg dose did increase peripheral ALC and multiple subsets of T cells, thus can potentially provide benefit to the patients; 3) there are large differences between 480 µg/kg, 960 µg/kg, and 1200 µg/kg doses that may allow detection of the differences in pharmacodynamic parameters (e.g. peripheral ALC and TILs) between the three dose levels.

Hence, based on the preclinical and clinical data, 480, 960, and 1200 µg/kg are selected for testing in this study.

5.3. 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 dose level. When more than 1 DLT occurs in ≤ 6 subjects in a dose level, dose escalation will be stopped, and this dose level 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 Section **6.2**. The DLT evaluation period is the first 21 days (3 weeks) of study treatment (Cycle 1, Day 1 to 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 dose level 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, Inc.'s 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.

5.4. 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: Ovarian Cancer

In Stage 1, up to 17 evaluable subjects per arm will be enrolled and treated. If at least one subject achieves objective response (complete response [CR] or partial response [PR]) 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 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.

5.5. Subject Expansion (Arm IVa and Va)

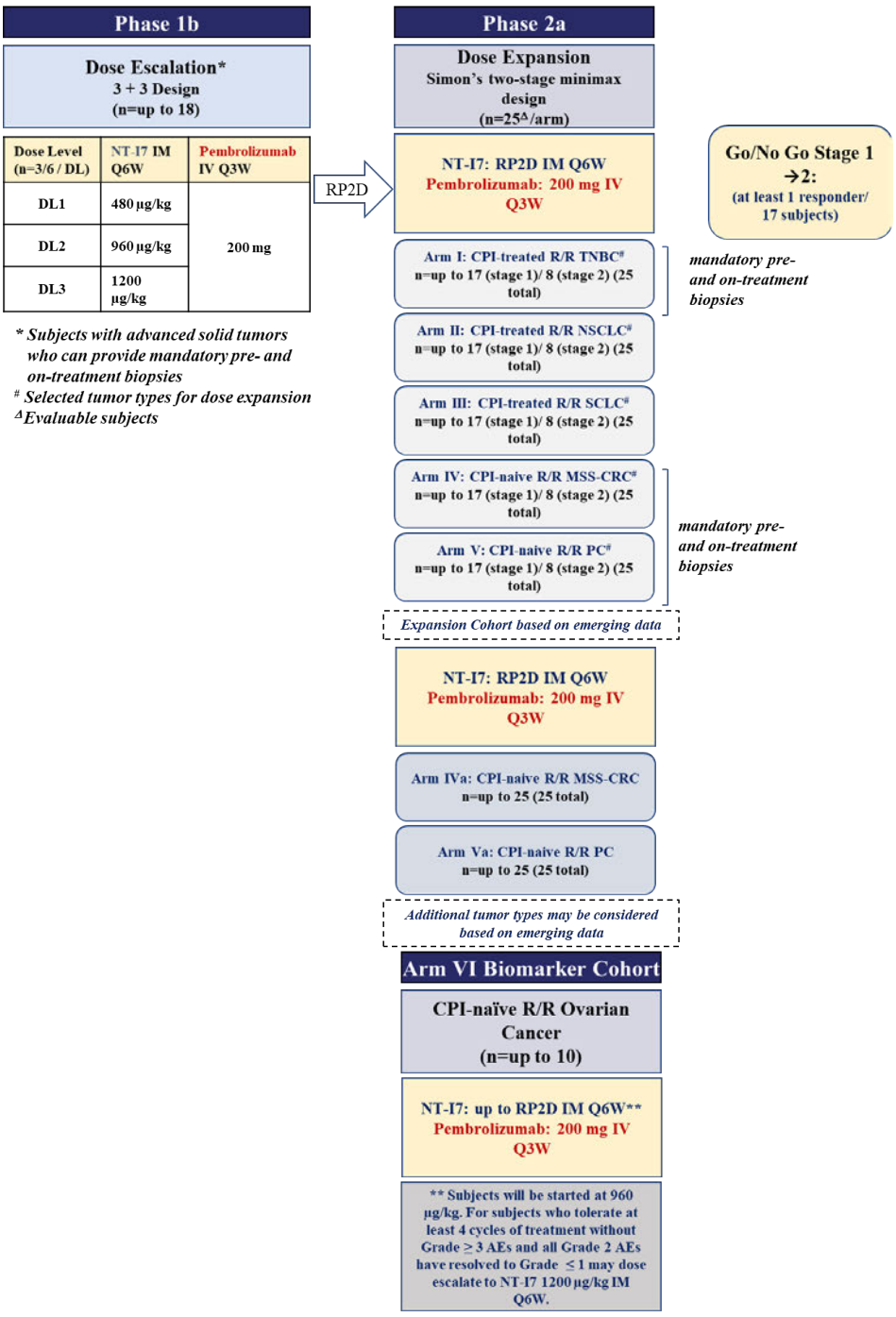
The Subject Expansion Cohort is designed to further assess the clinical benefits of NT-I7 in combination with pembrolizumab in subjects enrolled in the 2 selected cohorts based on emerging data. Subjects will receive Pembrolizumab at 200 mg IV Q3W and NT-I7 1200 μg/kg IM Q6W.

5.6. Biomarker Cohort

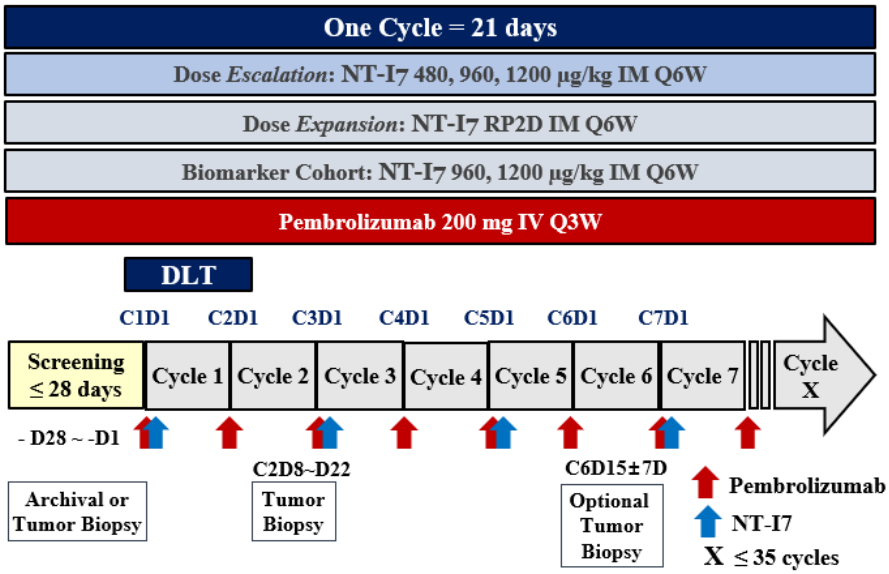
The Biomarker Cohort is designed to assess the correlation between tumor infiltrating lymphocytes (TILs) and clinical benefits of NT-I7 in combination with pembrolizumab in subjects with CPI-naïve R/R Ovarian Cancer (OC). Up to 10 evaluable subjects will be enrolled in this cohort. The starting dose 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.

5.7. Study Schema



5.8. Treatment Schema



CT/MRI

Radiological tumor assessments will be conducted every 2 cycles (6 weeks ±1 week) during the first 6 months, and every 3 cycles (9 weeks ±1 week) thereafter. Confirmatory scans must be performed at >4 weeks after initial assessment of response to confirm a best response of CR or PR, whenever disease progression is suspected (e.g., symptomatic deterioration), and at End of Treatment visit. If disease progression is identified by RECIST 1.1, a second scan will be scheduled 4-8 weeks later to confirm disease progression by iRECIST. (See Section 13 and Appendix A for details).

Tumor Biopsy

Pre-treatment biopsy/tissue collection (fresh) must be obtained within 28 days prior to Cycle 1, Day 1, unless archival tissue is available. On-treatment tumor biopsy must be obtained within 7 days of Cycle 2, Day 15 (i.e., between C2D8 and C2D22) and an optional tumor biopsy may be performed for the biomarker cohort or expansion cohorts IVa and Va on C6D15 ±7 days.

6. Study Treatment

NT-I7 and Pembrolizumab

6.1. Study Treatment Administration

Reported AE and potential risks are described in Section **11.1.** Appropriate dose modifications are described in Section **8.1** and **8.2**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Treatment will be administered on an outpatient basis.

Table 2: Study treatment details

Study Treatment	Dosage Formulation	Unit Dose Strength	Dosage Level(s)	Route	Regimen or Treatment Period	Sourcing
NT-I7	Solution for injection	25 mg/mL	Dose in µg/kg[a] Q6W	IM injection	Day 1 of alternate cycle	Provided centrally by Sponsor
Pembrolizumab (MK-3475)	Solution for infusion	100 mg/vial	200 mg Q3W	IV infusion	Day 1 of every cycle	Provided centrally by Sponsor

Abbreviations: IM=intramuscular; IV=intravenous.

[a]Refer to Sections **5.4**, **5.5** and **5.6** for assigned dose level.

6.1.1. NT-I7

Chemical Formula: $C_{4012}H_{6350}N_{1104}O_{1238}S_{42}$

Structural Formula: NT-I7 is a fusion protein comprising human IL-7 fused to the human IgD hinge region. This in turn is fused to the N-terminal region of CH2 from IgD and two key regions of the antibody IgG4: C-terminal region of CH2 and the entire CH3 region.

6.1.1.1. NT-I7 Pharmaceutical Information

NT-I7 protein is produced by inserting the gene expressing rhIL-7-hyFc into the eukaryotic expression vector pAD15 at the Multiple Cloning Site. The CHO cell line DG44 is used to produce NT-I7. NT-I7 has a molecular weight of 104 KDa and is composed of 400 amino acids with 155 amino acids for IL-7 and 30 for the IgD hinge, 8 for IgD the CH2 domain, and 207 for the IgG4 region. NT-I7 contains 11 disulfide bonds, 1 O-glycosylation and 3 N-glycosylation sites.

Pharmaceutical Properties: NT-I7 is supplied in a sterile, preservative-free liquid form in a single-use vial. One vial (1.0 mL) contains 25 mg per 1 mL of the active ingredient of the finished drug product. The purity of the active ingredient must be 89.0% or higher based on size-exclusion ultra-high-performance liquid chromatography (SE-UHPLC) testing and 90.0% or

higher based on reverse-phase high-performance liquid chromatography (RP-HPLC) testing. The NT-I7 finished drug product should be a colorless, clear solution and should not contain any particulate matter that can be observed visually.

Dosage Form: In addition to the active ingredient NT-I7, each vial contains sucrose, D-sorbitol, tri-sodium citrate dehydrates, citric acid monohydrate and Polysorbate 80 as a stabilizer and buffer. These ingredients meet the specification criteria of the European pharmacopeia (Ph. EUR). NT-I7 is supplied in a 1.0 mL vial package at a concentration of 25 mg protein/mL. The finished drug product solution contained in the vial is a liquid injection dosage form at pH 5.0±0.5 and a colorless, clear solution. There should not be any floating particulates under gross observation. For information on the injection sites, please refer to *NT-I7 Pharmacy Manual*.

Storage and Handling of NT-I7: Vials that contain NT-I7 must be kept refrigerated at 2~8℃. NT-I7 vials should NEVER BE FROZEN. It is recommended that vials are protected from direct light until the time of use.

Route of Administration: IM injection. DO NOT SHAKE vials before injection. A vial is restricted to 1 subject and to 1 day of treatment.

6.1.1.2. NT-I7 Dosing

Subjects will receive NT-I7 according to the following dose escalation schedule. Dose escalation will proceed within each dose level as described in Section **5.3**.

The NT-I7 dose will be administered 45 (±15) minutes after Pembrolizumab on all days where concurrent administration is planned. NT-I7 dose administered will be determined using the subject's body weight. Refer to the *NT-I7 Pharmacy Manual* for details.

NT-I7 will be injected intramuscularly. Guidelines for IM injection by the research nurse or investigator are described in the *NT-I7 Pharmacy Manual*.

On the odd-numbered cycles as pembrolizumab and NT-I7 are administered, vital signs need to be obtained within 60 minutes prior to the start of the pembrolizumab infusion and repeated after the completion of the infusion but before the NT-I7 injection.

6.1.2. Pembrolizumab

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. [*NT-I7 to be administered 30-60 minutes post administration of pembrolizumab on days where concurrent administration is planned].*

Pembrolizumab will be administered as a dose of 200 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).

On the even-numbered cycles (only pembrolizumab administered), vital signs need to be obtained within 60 minutes prior to the start of the pembrolizumab infusion.

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

6.2. Dose-Limiting Toxicity

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.

Dose-limiting toxicity 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.

6.2.1. DLT criteria

1. Grade 4 non-hematologic toxicity (not laboratory).
2. Grade ≥ 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care
3. Grade ≥ 3 rash lasting ≥ 5 days
4. Grade 4 neutropenia lasting ≥ 5 days
5. 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.
6. 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.
7. 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.
8. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Clinically significant medical intervention is required to treat the subject, or
   - The 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.

9. 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.
10. Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
11. Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
12. Grade 5 toxicity.

Once all subjects in a dose level have completed the 3-week (21 days) DLT window, the AEs will be assessed by the DMC, which includes the Protocol PI, Study Medical Monitor, Study Statistician, and Study Sponsor's designee.

The subjects must complete the full 3-week DLT window to be considered evaluable for DLTs. Subjects who discontinue from the study before completion of the full 3-week DLT window for reasons other than the occurrence of a DLT (e.g., withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

All subjects will be monitored for occurrence of DLT. Monitoring of all safety and toxicity data is done by the PIs, the study Sponsor and/or designee on a real-time basis as data are entered into the electronic data capture (EDC) system. All participating sites must notify the protocol PI and the Sponsor or designee when a DLT has occurred.

6.3. Subject Replacement

Subjects who receive at least 1 dose of the investigational treatment will be considered evaluable for safety and included in the overall safety analysis.

Subjects who discontinue from the study before completion of the full 3-week DLT window for reasons other than the occurrence of a DLT (e.g., withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

6.4. Discontinuation of Study Intervention, Subject Discontinuation/Withdrawal, and Study Termination

6.4.1. Discontinuation of Study Intervention

In the absence of treatment delays due to AE(s), treatment with NT-I7 and pembrolizumab may continue for approximately 2 years or up to 35 cycles of study treatment relative to the date of the 1st dosing or until one of the following criteria applies:

- Disease progression warranting alternative systemic therapy

***Note**:* Subjects with RECIST-defined progressive disease (PD) who are otherwise stable without symptomatic progression should continue study treatment until the next radiographic imaging time point (at least 4 weeks after the prior assessment of PD) to assess for possible pseudo-progression.

Discontinuation from treatment does not represent withdrawal from the trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the Investigator, should any untoward effect occur. In addition, a subject may be discontinued from treatment by the Investigator or the Sponsor, if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.
A subject may be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment
- The Investigator believes that for safety reasons or tolerability reasons (e.g., AE) it is in the best interest of the subject to discontinue study drug.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AEs (e.g., those meet the DLT criteria or other adverse events which can jeopardize patient safety per enrolling physician or considered unacceptable by the subject)
- Progressive disease confirmed radiographically.
    - ***Note:*** *In the case of suspected pseudoprogression, patients will be advised to continue treatment beyond initial RECIST 1.1-defined PD while waiting for confirmation of PD, provided they are clinically stable (per iRECIST)*. Investigators are recommended to consult with the Sponsor designee regarding individual cases.
- Treatment interruption lasting >12 weeks (see Section **8.1.1**)
- The patient becomes pregnant. Refer to Section **11.8**.
- Noncompliance with study procedure requirements or study drug administration (e.g., non-compliance with study visits and miss too many drug administrations).
- The subject persistently uses a disallowed medication as discussed with the Sponsor's designee.
- Discontinuation of treatment may be considered, at the discretion of the treating physician per criteria below, but continue to be monitored in the study for any of the following reasons:
    - Recurrent Grade 2 pneumonitis
    - Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and had at least 2 treatments of NT-I7 beyond the date when the initial CR was declared. Completion of up to 35 treatments (or 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 **8.2.**

The reason(s) for protocol treatment discontinuation, the reason(s) for study removal and the corresponding dates must be documented in the CRF.

If a subject discontinues study drug for any reason (except withdrawal of consent from the study), end of treatment/early withdrawal assessments should be obtained as soon as possible and follow up assessments should be obtained according to SOA. Subjects who permanently discontinue study treatment for reasons other than objective RECIST 1.1 and iRECIST disease progression should continue to have scans performed as scheduled, at the investigative site or locally, up to one year after discontinuation of study treatment. Standard of care disease assessments will be collected until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent or end of study, whichever occurs first.

Subjects removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE; in addition, the subjects will be followed for disease status and overall survival, as described above.

6.4.2. Subject Discontinuation/Withdrawal from Study

Subjects have the right to withdraw from participation in the study at any time and any reason without prejudice to their future medical care by the investigator or at the institution. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.
A subject will be withdrawn from the study for any of the following reasons:

- Subject does not meet study eligibility criteria (“screen failure”)
- Withdrawal of consent by subject or subject’s legally acceptable representative
- Lost to follow up
- Death

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document.

Withdrawal of Consent
If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed unless the Subject agrees to take part in the end of treatment visit. Subject also has the option to partially withdraw from active participation in the study and scheduled visits, but may allow status followup via telephone or medical record review.

Lost to Follow-up
A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A subject cannot be deemed lost to follow-

up until all reasonable efforts made by the study site personnel to contact the Subject are deemed futile.

- The study site personnel must attempt to contact the subject to reschedule the missed visit as soon as possible, to counsel the subject on the importance of maintaining the assigned visit schedule, and to ascertain whether the subject wishes to continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every reasonable effort to regain contact with the subject (where possible, 3 telephone calls, emails, fax, and if necessary, a certified letter to the subject's last known mailing address). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable despite every reasonable effort to regain contact by the site, they will be considered lost to follow-up and withdrawn from the study.

6.4.3. Study Termination

The Sponsor reserves the right to terminate the study at any time for any reason. If this decision is made, all subjects will be required to be discontinued from treatment and complete the end of treatment study visit.

6.5. Study Treatment Beyond Progression

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

At the investigator's discretion, a participant may continue on study intervention beyond radiological progression as defined by RECIST 1.1 if the clinical condition of the participant is stable or the participant is improving symptomatically, and the investigator expects continued clinical benefit for the participant until subsequent progression determined by iRECIST criteria (Appendix A – Assessment of Disease).

In participants who have initial evidence of radiological PD by RECIST 1.1, it will be at the discretion of the investigator whether or not to continue a participant on study treatment until repeat imaging is obtained to determine whether participant's disease is progressing or the initial evidence represents a 'pseudoprogression or tumor flare'. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study treatment until tumor assessment is repeated ≥4 weeks later in order to confirm PD by iRECIST.

Per iRECIST (Appendix A – Assessment of Disease) disease progression should be confirmed by the site in 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the clinically stable definition as Appendix A – Assessment of Disease, including. absence of

symptoms and signs indicating clinically significant progression of disease. Subjects should remain on the study and continue to be monitored according to the Schedule of Assessments.

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule.

If PD is confirmed, participants will be discontinued from study treatment. If a participant has iCPD as defined in Appendix A, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following 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 Table 6.

6.6. Duration of Follow-Up and End of Study

The active study will end when the last subject completes the 90-day Safety Follow-up visit, approximately 2 years after enrollment.

End of treatment (EOT) visit should be performed within approximately 7 days after disease progression determination, treatment discontinuation, or immediately before initiation of any other cancer therapy, whichever is earlier.

Safety Follow-up visit should be performed 30 (± 7) days and 90 (± 7) days after the last administration of either agent.

Subjects who complete all 35 cycles of treatment or permanently discontinue study treatment for reasons other than objective disease progression confirmed by RECIST 1.1 and iRECIST should continue to have RECIST scans performed every 9 weeks (± 7 days), at the investigative site or locally, up to one year after discontinuation of study treatment. Standard of care disease assessments will be collected until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent or end of study, whichever occurs first.

After disease progression or start of new anticancer treatment, subjects will be followed for survival every 90 days (± 7 days) until death, lost to follow-up, withdrawal of consent or end of the study, whichever occurs first. Survival follow-up can be done either by in-person visit or by telephone assessment.

Subjects removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE; in addition, the subjects will be followed for disease status and overall survival, as described above.

7. Study Procedures and Assessments

7.1. Informed Consent

A copy of the signed and dated ICF will be provided to the subject. The original ICF will be retained by the Investigator. Informed consent must be obtained prior to performing any study-specific procedures.

For subjects who wish to continue on study treatment beyond confirmed iRECIST-defined PD, a second ICF, if applicable, will be provided to the subject.

7.2. Study Procedures

Schedule of Assessments shows all procedures to be conducted at the screening visit, on-treatment, end of treatment, and follow-up visits. Refer to Section **7.4.**

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the proper nominal time.

All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

7.3. NT-I7 Pharmacokinetics

PK samples will be collected from all Phase 1b and Phase 2a subjects. Serial samples will be assessed following the PK timepoints in Table 3.

Note: *The precise NT-I7 administration time and the precise PK draw time should be recorded accurately and prospectively to fully interpret these values.*

Table 3: Pharmacokinetic Timepoints (All Subjects in Phase 1b and Phase 2a, and Biomarker Cohort)

Treatment Cycle/Visit	**Cycle 1**					**Cycle 2**	**Cycle 3**		**Cycle 4**	**Cycle 5**	**Subsequent Cycles (Repeat up to 2 years)**	**End of Tx**
Scheduling Window	**Day 1**			**Day 2**	**Day 8 ± 2 days**	**Day 1 ± 3 days**	**Day 1 ± 3 days**	**Day 8 ± 3 days**	**Day 1 ± 3 days**	**Day 1 ± 3 days**	**Day 1 ± 3 days**	
Hours	0 h	2 h (±15mins)	6 h (±30mins)	24 h (±1h)								
Pharmacokinetics* (Phase 1b) & Biomarker Cohort	X[a]	X[b]	X[b]	X[b]	X	X[a]	X[a]	X	X[a]			X
Pharmacokinetics* (Phase 2a)	X[a]	X[b]	X[b]		X		X[a]	X		X[a]	X[a]	

[a]To be collected prior to study agent(s) administration on a dosing day.
[b]Blood draws are timed after NT-I7 administration is complete, not completion of pembrolizumab infusion.
*Details on blood collection, handling, and shipping are provided in the *NT-I7 Laboratory Manual*.

7.4. Schedule of Assessments

	Phase 1b and 2a																	
Treatment (Tx) Cycle/ Visit	**Screening**	**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**		**Subsequent Cycles (Repeat up to 2 years)**	**End of Tx[22]**	**Post Tx Follow U**		
																Safety FU[23]		**Survival FU[28]**
Scheduling Window	Within 28 days	Day 1	Day 2	Day 8 ±2 days	Day 1 ±3 days	Day 8 ±2 days	Day 15 ±7 days	Day 1 ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 1 ±3 days	Day 1 ±3 days	Day 15 ±7 days	Day 1 ±3 days		30 days after last dose ±7 days	90 days after last dose ±7 days	Every 90 days after last dose ±7 days
Pembrolizumab[1]		X			X			X		X	X	X		X				
NT-I7[2]		X						X			X			Odd Cycles				
Administrative Procedures																		
Informed consent[3]	X																	
Demographics	X																	
Medical history	X																	
Prior and concomitant medications[4]	X	X		X	X			X	X	X	X	X		X	X	X	X	
Clinic Procedures/Assessments[#]																		
Physical exam[5]	X	X			X			X		X	X	X		X	X	X	X	
Performance Status[6]	X	X		X	X			X	X	X	X	X		X	X	X		
Vital signs[7]	X	X		X	X			X	X	X	X	X		X	X	X		
Height[8]	X																	
Weight	X	X			X			X		X	X	X		X	X	X		
Adverse events review[9]	X	X	X[27]	X	X			X	X	X	X	X		X	X	X	X	
12-lead EKG[10]	X	X									X			X	X			
Cardiac enzymes (Troponin ([Tnl or	X	X									X			X	X			

Phase 1b and 2a																		
Treatment (Tx) Cycle/ Visit	**Screening**	**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**		**Subsequent Cycles (Repeat up to 2 years)**	**End of Tx[22]**	**Post Tx Follow U**		
																Safety FU[23]		**Survival FU[28]**
Scheduling Window	Within 28 days	Day 1	Day 2	Day 8 ±2 days	Day 1 ±3 days	Day 8 ±2 days	Day 15 ±7 days	Day 1 ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 1 ±3 days	Day 1 ±3 days	Day 15 ±7 days	Day 1 ±3 days		30 days after last dose ±7 days	90 days after last dose ±7 days	Every 90 days after last dose ±7 days
TnT]) and CK-MB)[10]																		
Echocardiogram[30]	X	X									X			X	X			
Cardiologist visit[30]	X	X									X			X	X			
CBC w/diff, platelets[11]	X	X		X	X	X[26]		X	X	X	X	X		X	X	X		
Serum chemistry[12]	X	X		X	X	X[26]		X	X	X	X	X		X	X	X		
PT/INR and aPTT	X	X													X			
Thyroid Function[13]	X	X						X			X			Odd cycles	X			
Serum or Urine Pregnancy Test[14]	X	X						X			X				X	X		
Urine Analysis[15]	X	X			X			X		X	X	X		X	X			
Efficacy Measurements																		
Tumor evaluation (CT/MRI)[16]	X				X					RECIST 1.1 and iRECIST algorithm: Every 6 weeks (± 1 week) starting at Cycle 2, Day 1 for the first 6 months, then every 9 weeks (± 1 week) until disease progression or study discontinuation.					X			
Tumor Biopsies/Archival Tissue Collection																		
Tumor Biopsy	X[17]						X[29]						X[24]					
Correlative Studies[#]																		
Immunogenicity[18]		X			X			X			X			Every 4 cycles[18]	X		X	

	Phase 1b and 2a																	
Treatment (Tx) Cycle/ Visit	**Screening**	**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**		**Subsequent Cycles (Repeat up to 2 years)**	**End of Tx[22]**	**Post Tx Follow U**		
																Safety FU[23]		**Survival FU[28]**
Scheduling Window	Within 28 days	Day 1	Day 2	Day 8 ±2 days	Day 1 ±3 days	Day 8 ±2 days	Day 15 ±7 days	Day 1 ±3 days	Day 8 ±3 days	Day 1 ±3 days	Day 1 ±3 days	Day 1 ±3 days	Day 15 ±7 days	Day 1 ±3 days		30 days after last dose ±7 days	90 days after last dose ±7 days	Every 90 days after last dose ±7 days
Pharmacokinetics[19]	**Refer to Table 3 for PK sampling**																	
Immunophenotyping[20]		X		X	X	X[26]		X	X	X			X[25]		X			
Cytokines		X		X		X[26]		X	X	X			X[25]		X			
TCR-Seq Analysis		X[21]					X[21]						X[25]					

#Unless otherwise specified, all clinic procedures and sample collection are to be done prior to NT-I7 and/or pembrolizumab dosing. More details in the *NT-I7 Laboratory Manual*.

[1]Pembrolizumab should be administered on Day 1 of each three-week cycle after all procedures/assessments have been completed.
[2]NT-I7: Dose as assigned; once every 6 weeks, starting Cycle 1, Day 1. NT-I7 should be dosed after pembrolizumab on concurrent treatment days.
[3]Written consent must be obtained prior to performing any protocol specified procedure.
[4]Prior medications – Record all medications (prescription and over-the-counter [OTC]) taken within 30 days of Screening visit. Concomitant medications – Enter all medications (prescription and OTC) taken between 7 days prior to Cycle 1, Day 1 through the Safety Follow-up visit.
[5]Full physical exam is required during Screening, Day 1 of every cycle, End of Treatment, and Safety Follow-up visits. A directed physical exam may be performed on other days as clinically indicated.
[6]Performance status must be assessed per ECOG Performance Scale criteria.
[7]Vitals (blood pressure, heart rate, respiratory rate, temperature) to be collected in a standardized manner in a sitting position after the subject has rested comfortably for ~5 minutes. On the odd-numbered cycles (pembrolizumab and NT-I7), vitals need to be obtained within 60 minutes prior to the start of the pembrolizumab infusion AND repeated after the completion of the pembrolizumab infusion, but before the NT-I7 injection. On the even-numbered cycles (pembrolizumab only), vitals need to be obtained within 60 minutes prior to the start of the pembrolizumab infusion.
[8]Height is measured on the first visit during Screening only.
[9] All AEs, including those meeting serious criteria, from the time of consent through the 30-day safety follow-up visit, and AEs meeting serious criteria only from 30 days following cessation of study treatment to 90-day safety follow-up visit. See Section **11** for additional details on reporting of AEs.
[10] Duplicate EKG, at least 5 minutes apart, and serum cardiac enzyme levels (Troponin (TnI or TnT) and CK-MB) must be obtained at Screening, C1D1, every 4 cycles (i.e., C5D1, C9D1,..), and End of Treatment. A patient should be assessed by a PI or a local cardiologist to determine if the EKG and the serum cardiac enzyme levels are clinically significant. If either is found to be clinically significant, see footnote 30.
[11]Hematology includes complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential (neutrophil count including lymphocyte, monocyte, eosinophil, basophil counts and bands), absolute neutrophil count (ANC), and platelet count.

[12]Chemistry includes (but is not limited to) sodium, potassium, calcium, phosphorus, chloride, magnesium, bicarbonate, blood urea nitrogen (BUN) or urea, serum creatinine, glucose, uric acid, albumin, total protein, alkaline phosphatase, lactate dehydrogenase, bilirubin (indirect and direct), aspartate serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum pyruvic transaminase (ALT/SGPT).

[13]Thyroid function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as free T4)

[14]Serum pregnancy test to be performed at the Screening visit for all females except those surgically sterile or 2 years postmenopausal. Subsequent serum or urine pregnancy tests could be performed as noted or per Investigator's discretion. If the serum screening pregnancy test is performed > 72 hours before first dose, a serum or urine pregnancy test should be repeated prior to dosing.

[15]Urinalysis (a urine dipstick may be used) at Screening and D1 of each cycle.

[16]Baseline CT/MRI tumor imaging must be performed within 28 days prior to first dose for all subjects. Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within the allotted screening window. The exact same image acquisition and processing parameters should be used throughout the study. The first on-study imaging time point will be performed 6 weeks (± 1 week) or earlier if clinically indicated, regardless of any treatment delays, for up to 6 months, and every 9 weeks (± 1 week) thereafter. Brain and/or bone lesions may be scanned if applicable. (**Note:** Subjects do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks after the previous scan.) See Section **13** and Appendix A – Assessment of Disease for further information.

[17]Biopsy will be performed during screening for those subjects who did not have enough archival tumor tissue and are required to have pre-treatment tumor biopsy per protocol.

[18]Samples for immunogenicity assays shall be collected pre-dose from all study subjects in Phase 1b, Biomarker Cohort, and in 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. Testing may be conducted as indicated above, and repeated at 90-day follow up visit, if positive at the end of treatment visit.

[19]For sampling details of PK, please refer to Table 3. Additional information on handling and shipping are provided in the *NT-I7 Laboratory Manual*.

[20]Whole blood will be collected for the multispectral immunophenotyping to obtain absolute cell counts for CD4+ and CD8+ T-cell subsets and activation states, NK cells, B cells, and other cell types as necessary.

[21]TCR-seq analysis will be performed on both whole blood (pre- and on-treatment) for all Phase 1b and selected Phase 2a arms - TNBC (Arm I), MSS-CRC (Arm IV and Arm IVa), PC (Arm V and Arm Va), and the Biomarker Cohort (only for subjects who have dose of NT-I7 increase to 1200 µg/kg at C5D1). TCR-seq whole blood sample should be taken pre-dose at C1D1 visit. On-treatment whole blood sample should be taken at the same visit (pre- or post-biopsy) as on-treatment tumor biopsy collection (C2D15±7 days).

[22]End of Treatment visit will occur approximately anytime within 7 days after disease progression determination or treatment discontinuation.

[23]Safety follow-up visits will be performed in clinic visit will be performed every 30 days and 90 days after last dose of treatment.

[24] Optional tumor biopsy at Cycle 6, Day 15 (± 7 days) only for CPI naïve R/R OC Biomarker Cohort (only for subjects who have dose of NT-I7 increase to 1200 µg/kg at C5D1), CPI-naïve R/R MSS-CRC Arm IVa, and CPI-naïve R/R PC Arm Va.

[25] Applicable only for CPI naïve R/R OC Biomarker Cohort (only for subjects who have dose of NT-I7 increase to 1200 µg/kg at C5D1), CPI-naïve R/R MSS-CRC Arm IVa, and CPI-naïve R/R PC Arm Va.

[26] Optional visit applicable only for the CPI naïve R/R MSS-CRC Arm IVa and CPI-naïve R/R PC Arm Va expansion cohorts.

[27] Visit must be performed in person during Phase 1b for PK sampling and may be performed in clinic or by telephone during Phase 2a.

[28] Survival follow-up by telephone will be performed every 90 days starting 90 days after Safety follow-up day 90 until death, lost to follow up, withdrawal of consent, or end of study, whichever occurs first, to find out the survival status, new anti-cancer treatments and the outcome of any ongoing adverse event(s).

[29] For all Phase 1b dose-escalation and selected Phase 2a arms - TNBC (Arm I), MSS-CRC (Arm IV and Arm IVa), PC (Arm V and Arm Va), and Biomarker Cohort, mandatory biopsies are required pre- and on-treatment. On treatment biopsies will be taken at C2D15 (± 7 days). If C3D1 (C2D15 + 7 days) is decided for the biopsy, the biopsy has to be taken before dosing on Cycle 3.

[30] If either the EKG or serum cardiac enzyme levels are clinically significant, an echocardiogram must be performed and the patient must be assessed by a local cardiologist to rule out the potential presence of myocarditis and to ensure there are no clinically significant abnormalities in the echocardiogram before enrolling in or continuing treatment. The next dosing will be suspended during the follow-up period until confirmation is obtained through an echocardiogram.

8. Dosing Delays/ Dose Modifications

The National Cancer Institute (NCI) CTCAE Version 5.0 will be used to grade AEs. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in this section.

Subjects will be evaluated for AEs (all grades), SAEs, and AEs requiring study drug dose modification, interruption, or discontinuation at each study visit for the duration of their participation in the study.

8.1. Dose Modification of NT-I7

Clinical experience has demonstrated that development of autoimmune inflammatory conditions is a general risk with therapeutics intended to enhance anti-tumor T-cell responses. Such irAEs have been described for virtually all organ systems and include, but are not limited to, colitis, hepatitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity, and rash.

Risks of autoimmunity associated with NT-I7 are theoretical and yet not fully evaluated in the clinical setting. Due to this potential risk of NT-I7 to induce autoimmune conditions, subjects with a history of autoimmune disease will be excluded from this study.

The risk of development of autoimmune inflammatory condition related to NT-I7 seems relatively low. None of the irAEs were reported in previous clinical studies with rhIL-7, or with NT-I7 including the FIH study completed in normal healthy individuals, and solid tumor subjects (Study No. GX-I7-HV-001 and Study No. GX-I7-CA-003).

Nevertheless, however, given the limited clinical experience with NT-I7, immune-related toxicities associated or possibly associated with NT-I7 should be closely monitored and carefully managed according to standard medical practice (e.g., thyroid hormone replacement for autoimmune hypothyroidism). Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology. Although most irAEs observed with immune modulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (69). Discontinuation of NT-I7 may not have an immediate therapeutic effect, and there is no available antidote for NT-I7. The primary approach to mild irAEs (Grades 1−2) is supportive and symptomatic care. In severe cases, irAEs may be acutely managed with systemic corticosteroids, mycophenolate or TNF-α antagonists (40, 69-85).

Dose modifications of NT-I7 for Adverse Events: AEs from NT-I7 are expected to be mild and infrequent, transient and Grade 2 or less (as noted in the AE list, Section **11.1.1**. If a subject experiences a clinically significant and/or unacceptable toxicity, dosing should be interrupted, or reduced or discontinued (see below for detailed guidance), and supportive therapy administered per standard clinical practice.

A maximum of 2 dose reductions will be allowed for an individual subject. If the second dose reduction is not tolerated, study treatment should be permanently discontinued, and the subject should be followed up for safety (see Section **11.3.1**). The lowest dose that may be administered is:

- NT-I7 480 µg/kg Q6W

For a Grade 1 AE, no dose modification is needed. Increase monitoring of clinical signs/symptoms and laboratory assessments as needed and treat each of the toxicities per standard of care and/or institutional guidance. For Grade 1 AE of myasthenia gravis, NT-I7 treatment may be withheld until resolved (see Section **8.1.1** for criteria to resume treatment) or discontinued permanently.

For a Grade 2 AE related to NT-I7, withhold administration of NT-I7 until the AE is resolved to ≤ Grade 1 (see Section **8.1.1** for criteria to resume treatment), then resume at the same dose level.

For a Grade ≥3 AE related to NT-I7, if it is a 1st appearance, withhold administration of NT-I7 until the AE is resolved to ≤ Grade 1 (see Section **8.1.1** for criteria to resume treatment), then decrease one dose level (e.g., to 960 µg/kg IM Q6W if the last dose level prior to the AE was 1200 µg/kg IM Q6W, or to 480 µg/kg IM Q6W if the last dose level prior to the AE was 960 µg/kg IM Q6W); if it is a 2nd appearance, withhold administration of NT-I7 until the AE is resolved to ≤ Grade 1, then decrease one dose level (e.g., to 480 µg/kg IM Q6W if the last dose level prior to the AE was 960 µg/kg IM Q6W). The lowest dose that may be administered is 480 µg/kg IM Q6W. Dose re-escalation to a higher dose level, up to 1200 µg/kg IM Q6W, is allowed after being discussed with and approved by the Medical Monitor and the Sponsor.

For any grade of myocarditis, permanently discontinue NT-I7 treatment.

8.1.1. Criteria to Resume for Dosing

Subjects may resume treatment with NT-I7 when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for re-initiation of study treatment if discussed with and approved by the Medical Monitor and the Sponsor.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume study treatment after consultation with and approved by the Medical Monitor and the Sponsor.

Prior to re-initiating study treatment in a subject with a dosing delay lasting > 12 weeks (84 days) for NT-I7 or >6 weeks (42 days) for pembrolizumab, the NIT designee) must be

consulted and approves the re-initiation of study treatment. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 3 weeks or more frequently if clinically indicated during such dosing delays.

8.2. Dose Modification of Pembrolizumab

The toxicity of pembrolizumab could be accentuated by administration of NT-I7 and the component attributable to pembrolizumab and NT-I7 will be difficult if not impossible to sort out. Thus, the management of pembrolizumab will be used for the treatment of any AE. NT-I7 treatment will be discontinued when pembrolizumab must be **permanently discontinued.**

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab 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, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

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 NT-I7 alone, or to pembrolizumab alone, for adverse events listed in Table 4, both interventions must be held according to the criteria in .

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:

Subjects may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 4.

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

If the toxicities do resolve and conditions are aligned with what is defined in Table 4, the combination of NT-I7 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to NT-I7 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Table 4: 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 systemic immunosuppressive treatment may be considered if the irAEs are not controlled by corticosteroids. 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. If another episode of a severe adverse reaction occurs, permanently discontinue pembrolizumab.				
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	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and exclude other causes. Initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg	Monitor subjects for signs and symptoms of colitis and exclude other causes.

	Grade 4	Permanently discontinue	prednisone or equivalent) followed by taper	
Hepatitis	Grade 2	Withhold or discontinue based on severity of liver enzyme elevations.	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for changes in liver function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes.
	Grade 3 or 4		Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	T1DM		Initiate insulin replacement therapy for subjects with T1DM	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes

	Severe hyperglycemia	Withhold until metabolic control is achieved		
Adrenal insufficiency (primary and secondary) and Hypophysitis	Grade 2	Withhold	Administer corticosteroids for adrenal insufficiency and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes.
	Grade 3 or 4	Withhold or discontinue		
Hyperthyroidism	Grade 2	Continue	Manage symptomatically	Monitor for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grade 2, 3, 4	Continue	May be managed with replacement therapy without corticosteroids.	Monitor for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders
Nephritis	Grade 2	Withhold	Administer corticosteroids (prednisone 1–2 mg/kg or equivalent)	Monitor changes of renal function and exclude other causes.
	Grade 3 or 4	Permanently discontinue		

			followed by taper	
Severe skin reactions		Based on the severity of AE, withhold or permanently discontinue	Based on severity of AE, administer corticosteroids	Monitor for suspected severe skin reactions and exclude other causes. For signs and symptoms of SJS/TENS, refer the subject for specialized care for assessment and treatment.
Severe skin reactions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Administer corticosteroids with specialized care	
All Other irAEs	> Grade 1	Withhold	Based on severity of AE administer corticosteroids and taper upon improvement to Grade 1 or less, over at least one month. Administration of other systemic immunosuppressants can be	Ensure adequate evaluation to confirm etiology or exclude other causes
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

			considered if irAEs cannot be controlled with corticosteroid use.	

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-irAEs will be managed as appropriate, following clinical practice recommendations.

8.2.1. Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe infusion-reactions including severe hypersensitivity or anaphylaxis. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5: Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated **Grade 2** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• May continue to receive pembrolizumab with close monitoring	Premedication with antipyretic or antihistamine may be considered
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;	• **Stop Infusion.** Subject is permanently discontinued from further study drug treatment.	No subsequent dosing

hospitalization indicated for other clinical sequelae **Grade 4:** Life-threatening consequences; urgent intervention indicated		
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		

8.2.2. Other Allowed Dose Interruptions for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events and/or unforeseen circumstances not related to study therapy. Subjects should be placed back on study treatment within 3 weeks or 21 days of originally scheduled dose and within 42 days of previously administered dose, unless otherwise discussed with and approved by the Sponsor. The reason for interruption should be documented in the subject's study record.

9. Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study treatment or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor or Sponsor's assigned designee. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the Sponsor and the subject.

9.1. Prohibited Medications/Treatment

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than NT-I7 and pembrolizumab
- Radiation therapy
  Note: *Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.*
- Live/attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study up to 90 days following the last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, 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.
- Systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - Short-term oral or IV use in doses >10mg/day prednisone equivalent for the prevention of emesis is allowed after discussion with and approval by the Medical Monitor
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses >10mg/day prednisone equivalent for COPD exacerbations
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
  - In addition, the following glucocorticoid use is allowed:
    - For topical use or ocular use
    - Intra-articular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

  Note: *Inhaled steroids are allowed for management of asthma.*
- Immunostimulatory and immunosuppressive agents are prohibited.

Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

9.2. Medications Used with Caution

No data exist regarding the interaction of NT-I7 with drugs known to prolong the QT/QTc interval. Accordingly, subjects receiving these drugs while receiving NT-I7/pembrolizumab therapy should be closely monitored.

No data exist regarding the interaction of NT-I7 with commonly used vitamins, minerals, supplements, herbal and natural remedies. Accordingly, these drugs should be avoided, or used with caution at the investigator's discretion, and closely monitored while the subject is receiving the study treatment.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. For example, subjects can continue using medically prescribed marijuana/ Marinol for purposes such as cancer related fatigue, nausea, vomiting, appetite improvement etc. while participating in the study.
All concomitant medications will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 7 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of special interest or clinical interest (ECIs) as defined in Sections **11.4** and **11.6.**

10. Rescue Medications and Supportive Care

Subjects 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 **8.** (Table 4). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease, or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section **8** 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.

11. Adverse Events: Assessing and Reporting Requirements

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study product is also an AE.

All AEs that occur on study, within 30 days of the last administration of the study treatment, must be reported. The reporting timeframe for AEs meeting the criteria of SAE is described in Section **11**.

AEs are reported in a routine manner during the study using the EDC system. Additionally, certain AEs must be reported in an expedited manner for timelier monitoring of subject safety and care. The following list of AEs (Sections **11.1, 11.4,** and **11.6**) and the characteristics of an observed AE will determine whether the event requires expedited reporting to the Sponsor or designee.

Electronic monitoring of AEs will be done through the EDC system and/or via email reporting by each clinical site to the Sponsor and/or Sponsor's safety designee. Per GCP, all sites must enter data in a timely manner. AEs meeting the criteria of SAE in the EDC system will trigger immediate review and distribution as needed and required by regulatory authorities.

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs at the time points specified in the protocol and more frequently if clinically indicated.

11.1. Adverse Events and Potential Risks List

For a list of the adverse events and potential risks associated with NT-I7, please refer to the most recent version of the Investigator's Brochure.

11.2. Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For expedited reporting purposes only:

- AEs of Special Interest for the protocol are outlined in Sections **11.4** and **11.6**.

Attribution of the AE:

- Definite – The AE is *clearly related* to the study treatment.

- Probable – The AE is *likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE is *doubtfully related* to the study treatment.
- Unrelated – The AE is *clearly NOT related* to the study treatment.

11.3. Expedited Adverse Event Reporting

AE, SAEs, and other reportable safety events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

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 of AE, SAEs and other reportable safety events for outcome.

Expedited AE, including AESI, reporting for this study must be done by notifying the Sponsor and/or Sponsor's safety designee ***within 24 hours*** of the investigator or investigator designee knowledge of the event *via* the study EDC system and email (CHOSafety@prahs.com and NIT110@neoimmunetech.com) as stipulated.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the Sponsor designated CRO, ICON Safety Helpline, by telephone at +1 888 772 2215, fax ICON Safety Fax Line, +1 888 772 6919 or +1 434 951 3482. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into the data capture system by the original submitter at the site.

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

- All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment /allocation must be reported by the investigator, if the event causes the subject to be excluded from the study or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
- All AEs from the time of treatment/allocation through 30 days following cessation of study treatment or starting of new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment/ allocation through 90 days following cessation of study treatment or initiation of new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through 90 days following cessation of study treatment or initiation of new anticancer therapy, whichever is earlier, 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.

11.3.2. Expedited Reporting Guidelines

Use the study protocol number and the protocol-specific subject ID assigned during study registration on all reports. Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

***Note*: A death occurring within 90 days of the last administration of study agent requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.**

Death due to PD should be reported as **Grade 5 "Malignant neoplasm progression"** to be coded under the system organ class (SOC) "Neoplasms benign, malignant and unspecified (incl cysts and polyps)". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/ Intervention

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately (within 24 hours) report ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 Code of Federal Regulations [CFR] 312.64)
An AE is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

11.3.3. Routine Adverse Event Reporting

All AEs **must** be reported in routine study data submissions. **AEs reported expeditiously to the Sponsor and/or Sponsor's safety designee must <u>also</u> be reported in routine study data submissions.**

AE data collection and reporting, which are required as part of every clinical study, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. For this study the Adverse Event CRF is used for routine AE reporting.

11.4. Adverse Events of Special Interest in NT-I7

The following AEs are of special interest in subjects receiving NT-I7, as defined below and must be reported by the investigator expeditiously to the Sponsor and/or Sponsor's Safety designee irrespective of regulatory seriousness criteria and the relatedness to NT-I7.

Immune-related adverse event (irAE) is defined as an AE associated with drug exposure that is consistent with an immune-mediated mechanism of action when there is no clear alternate etiology. For events which are potentially immune-related, additional information such as serologic, immunologic, and histologic (biopsy) data and use of steroids or immunosuppressants will be used to support an irAE diagnosis.

- Potential drug-induced liver injury that includes an elevated ALT or AST ≥ 3 x ULN in combination with an elevated bilirubin ≥ 2 x ULN and, at the same time, an alkaline phosphatase (ALP) < 2 x ULN; no other reason can be found to explain the combination of increased AST or ALT, and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. (86)
- Conditions (regardless of grade) suggestive of an autoimmune disorder or immune-related adverse events (irAEs), including but not limited to hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies (including but not limited to thyroiditis, Type 1 diabetes mellitus, adrenal insufficiency), myocarditis, myositis/polymyositis, rheumatoid arthritis, vasculitis, neuritis, systemic lupus erythematosus, Sjogren's syndrome, multiple sclerosis, Guillain-Barre syndrome and myasthenia gravis
- Symptoms and signs suggestive of hypersensitivity, cytokine release, or infusion reaction syndromes with a different underlying pharmacological etiology
- Grade ≥2 diarrhea
- Grade ≥2 AST/ALT and Grade ≥2 total bilirubin elevation with constitutional symptoms
- Grade ≥3 hypoxia or dyspnea
- Grade ≥2 pleural effusion that is not due to the underlying disease (e.g., non-malignant pleural effusion)

11.5. Treatment of Overdose for NT-I7

For this study, an overdose of NT-I7 will be defined as any dose > 1440 µg/kg.

No specific information is available on the treatment of overdose of NT-I7. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

11.6. Events of Clinical Interest (ECI) in Pembrolizumab

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

Events of clinical interest in pembrolizumab studies include:

1. An overdose of pembrolizumab, as defined in Section **11.7**– 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 study 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 study.*

11.7. Treatment of Overdose for Pembrolizumab

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥5 times the indicated dose.

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

11.8. Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented via the EDC system. Any pregnancy occurring in a subject or subject's partner from the time of consent to 90 days after the last dose of study treatment must be reported and then followed for outcome. If a subject inadvertently becomes pregnant while on study drug treatment, the subject will be immediately discontinued from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience/important medical event (e.g., death, abortion, congenital anomaly, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, stillbirth or other disabling or life-threatening complication to the mother or newborn). Newborn infants should be followed until 30 days old.

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 and/or Sponsor's safety designee ***within 24 hours*** of the investigator's knowledge of the event via the study EDC system.

11.9. Use in Nursing Women

It is unknown whether NT-I7 and/or pembrolizumab 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, subjects who are breastfeeding are not eligible for enrollment.

11.10. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur after treatment with the study agents must be reported to the Sponsor and/or Sponsor's safety designee within ***24 hours*** of the investigator's knowledge of the event via the study EDC system. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

11.11. Second Malignancy

A *second malignancy* is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

12. Correlative Studies and Biomarker Evaluations

To explore the biological mechanisms and pharmacodynamic (PD) effects of the investigational treatment regimen, paired tumor biopsies, and peripheral blood samples will be utilized. Mandatory paired biopsy sampling will be obtained for all study subjects in Phase 1b, and study subjects in specific arms in Phase 2a. Peripheral blood will be obtained for PK, immunogenicity, and exploratory biomarker evaluations.

12.1. Tumor Tissue for Biomarker Analyses

A key exploratory objective of the study is to make preliminary assessment of biomarkers that may act as pharmacodynamic indicators or predictors of anti-tumor activity of NT-I7 in combination with pembrolizumab. Tumor biopsy sampling is mandatory for all study subjects in Phase 1b and study subjects in specific arms in Phase 2a (i.e., Arm I: CPI-treated R/R TNBC, Arms IV and IVa: CPI-naïve R/R MSS-CRC, Arms V and Va: CPI-naïve R/R PC), and the Biomarker Cohort. In these arms/cohorts, study subjects must have at least one tumor lesion that is accessible and feasible to biopsy and agree to provide paired biopsies in order to participate in this study, unless a written exemption is obtained from the Sponsor.

Tumor biopsy samples will be obtained from each study subject where biopsy sampling is mandatory. The first biopsy will be obtained within 28 days prior to initiation of study drugs in order to establish baseline characteristics of the tumor. Archival samples may be used in place of a fresh biopsy for the baseline treatment sample if the archival tissue was obtained after the last therapy, and is within 28 days of prior to initiation of the study treatment. A second biopsy (on-treatment biopsy) must be obtained within 7 days of Cycle 2, Day 15 (i.e., between C2D8 and C2D22), and before Cycle 3, Day 1 dosing in order to evaluate the effects of the study treatment on the tumor microenvironment. For subjects in CPI naïve R/R OC Biomarker Cohort, the CPI-naïve R/R MSS-CRC expansion IVa cohort and the CPI-naïve R/R PC expansion Va cohort, an optional tumor biopsy may be obtained at Cycle 6, Day 15 (± 7 days). For the Biomarker cohort, only in subjects who have dose of NT-I7 increased to 1200 μg/kg at C5D1. For subjects who discontinue from study early, every effort should be made to obtain the on-treatment biopsy. For detailed instructions on biopsy sample processing (collection, handling, and shipping), please refer to the *NT-I7 Laboratory Manual*.

Tumor biopsy samples will be evaluated for molecular and histological changes, particularly as these changes pertain to the inflammatory mechanisms. Exploratory biomarker analyses may include, but are not limited to, characterization of PD-L1 expression, quantitation of CD4+ and CD8+ tumor-infiltrating lymphocyte distribution, TCR repertoire analysis, and other molecular assessments.

12.2. Planned Peripheral Blood Biomarker Analyses

Study subjects are required to provide peripheral blood samples for PK, immunogenicity, and exploratory biomarker evaluations throughout their study participation as summarized in the Schedule of Assessments. Whenever possible, peripheral blood samples for these evaluations should also be collected during the 90-day FU period. For detailed instructions on peripheral blood research sample processing (collection, handling, and shipping), please refer to the *NT-I7 Laboratory Manual*.

Peripheral blood samples will be evaluated for the presence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) to NT-I7, as well as for pharmacokinetic analysis. Exploratory biomarker analyses on peripheral blood samples may also include, but not limited to, changes in circulating immune cell populations, cytokine measurements, and TCR repertoire analysis.

12.3. Other Procedures: Biopsy (core needle, punch, or surgical excision)

Specific details on the biopsy and its procedure, tissue collection, handling, and shipping are provided in the *NT-I7 Laboratory Manual*.

13. Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). 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. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a subject 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. **Note:** For the purposes of assessing tumor imaging, 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.

In general, imaging should include the chest, abdomen, and pelvis. See below for guidance regarding MRI Brain imaging.

Bone scans are also required for subjects with a history of bone metastases and/or for those subjects with new bone pain. Any supplemental imaging done to support a positive or negative bone scan, such as plain X-rays, may be acquired for correlation.

13.1. Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of treatment. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1.

For all subjects enrolled in Arm I (TNBC), Arm II (NSCLC), and Arm III (SCLC), a MRI brain imaging scan is preferred during screening. A brain scan at screening is required for any patient that has had brain metastasis in the past or presents with signs and/or symptoms suggestive of brain metastasis.

Subjects enrolled in Arm IV (MSS-CRC), Arm IVa (MSS-CRC), Arm V (Pancreatic Cancer), Arm Va (Pancreatic Cancer), and Biomarker OC Cohort must have an MRI brain imaging scan done during screening only if:

- The subject has known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- OR: the subject has sign/symptoms suggestive of brain metastasis

Note: *Subsequent MRI brain imaging is required only if:*

- *The screening brain scan is positive (has tumor lesion)*
- *The subject develops sign/symptoms suggestive of brain metastasis*

CT imaging is acceptable if MRI is medically contraindicated or cannot be scheduled in a timely manner.

13.2. Tumor Imaging During the Study

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 timing should follow calendar days and should not be adjusted for delays in cycle start dates. Imaging should continue to be performed until disease progression is identified by the investigator, or notification by the Sponsor, whichever occurs first.

Brain MRI is required during the study only if:

- The screening brain scan is positive (has tumor lesion)
- The subject develops sign/symptoms suggestive of brain metastasis

Brain CT imaging is acceptable if MRI is medically contraindicated or cannot be scheduled in a timely manner.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Appendix A – Assessment of Disease**)** disease progression should be confirmed by the site, 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects, who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Appendix A – Assessment of Disease. Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Subjects, who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Appendix A – Assessment of Disease, Table 6**.**

13.3. End of Treatment and Follow-up Tumor Imaging

For subjects who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation. If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

For subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging every 90 days (+/- 7 days) until the start of a new anti-cancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

Details on the assessment of disease using RECIST 1.1 and iRECIST can be found within Appendix A – Assessment of Disease**.**

13.4. Response Criteria

13.4.1. Evaluation of Target Lesions

Complete Response (CR). Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR). At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD). At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (**Note:** the appearance of 1 or more new lesions is also considered progressions).

Stable Disease (SD). Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

13.4.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

***Note**: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.*

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of 1 or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or PI).

13.4.3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR, or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized studies with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: *Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.*

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised

Abbreviations: CR=complete response; PD=progressive disease; SD=stable disease.

13.4.4. Duration of Response

Duration of response: The duration of response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.4.5. Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.4.6. Response Review

Radiological images may be collected for a possible review of response by an expert(s) independent of the study. Measurement of tumor response by a trained radiologist/nuclear medicine physician at each clinical site will be chronicled and reported unless or until a central expert review takes place.

Additional details are in the Appendix A – Assessment of Disease**.**

14. Data Management and Reporting

Data collection for this study will be done exclusively through an electronic clinical data management system. The Data Management Organization will utilize a core set of electronic Case Report Forms (eCRF) that are Clinical Data Acquisition Standards Harmonization (CDASH)-compliant (https://www.cdisc.org/standards/foundational/cdash). Customized eCRFs will be included when appropriate to meet unique study requirements. The data management organization will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

Access to the study is granted to all persons with the appropriate roles, as listed on the Delegation of Authority Sheet. Upon site activation, all persons with the appropriate roles will be sent a study invitation email. Site users will not be able to access the study until all required study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings).

For further details, please refer to the *Site Operations Manual*.

14.1. Responsibility for Data Submission

To provide evidence that the protocol has been followed, documentation of all procedures that are conducted under this protocol is required. In cases of screen failures, the following information must be documented within the source: demographic data (including at minimum sex, age and/or birth year, race/ethnicity, and informed consent date), the outcome of the eligibility assessment, the reason for the screening failure by criterion, and AE details.

It is the responsibility of the PI(s) at the site to ensure that all investigators and study staff at the clinical site understand the procedures for data submission per the protocol. Furthermore, the investigator or designee is responsible for submitting protocol-specified data and queries, including safety case processing queries, accurately and in a timely manner to the data management organization via the EDC system; these must be complete and verifiable with the source. The clinical site must appropriately maintain the source for the required time period – this ensures data integrity and traceability, and protects personal information of study subjects.

The data management organization is responsible for compiling and submitting data of all subjects to the study Sponsor. The EDC data and supporting documents should be available for the Sponsor/designee, auditors, and regulatory authorities to review/retrieve at any given time, as required by clinical trial agreements and GCP requirements.

Good Documentation Practices and ALCOA+ principles for data integrity must be followed for all essential documents and other clinical trial-related records. The Sponsor, the delegated CRO, and investigators must organize and securely retain data and other study records for the required period of time. These must be available if requested by regulatory authorities, to ensure the reliability of the trial's results.

14.2. Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the study Sponsor is solely responsible for determining whether the study and its results are subject to the requirements for

submission to the Clinical Trials Data Bank, https://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

14.3. Study Oversight

Responsibility for monitoring the clinical trial lies with the Sponsor or the delegated CRO. The purpose of monitoring is to ensure protection of subjects' human rights, safety, and well-being, to verify that the trial is conducted according to the current protocol and GCP, and that study data reported by the investigator are entered or available in a timely fashion, and are accurate, complete, and verifiable with source documents and other study-related records. Accordingly, the Sponsor or the delegated CRO will assign study monitor(s), who will monitor the study as detailed in planned monitoring procedures. Monitoring is scaled to data generation by sites.

The investigator and the clinical site are required to cooperate with monitoring and auditing by the Sponsor or delegated CRO, as well as inspections by the IRB/IEC and regulatory authorities. During monitoring, auditing, and inspections, all study-related records, including but not limited to source documents, training records, and delegation logs, must be provided upon request by Sponsor monitors/auditors, IRB/IEC, or regulatory authorities. The investigator must be available to discuss the findings of the monitoring visit or audit. When source documents are directly accessed, the confidentiality of subject identities must be protected in accordance with local and national regulations.

This protocol will adhere to the policies and requirements listed in the *Site Operations Manual*. Protocol waivers (documented prospective approval of requests from an investigator to deviate from the protocol) are prohibited for this study. For specific responsibilities of the PI, and NeoImmuneTech, Inc., please refer to the site-specific contract and the Form FDA1572.

Sponsor or Sponsor's designee is responsible for distributing all Investigational New Drug Application (IND) Action Letters or Safety Reports received from the study Sponsor, NeoImmuneTech, Inc., to all participating institutions for submission to their individual Institutional Review Boards (IRBs) for action as required.

Study drugs may be ordered by a participating site only after approved by the study Sponsor, NeoImmuneTech, Inc. and officially activated.

14.4. Subject Enrollment and EDC

Subject enrollment will be facilitated using the enrollment module in the EDC system. To access the enrollment module, the site user must be assigned the 'Enroll/Randomize subjects' responsibility on the Delegation of Authority Sheet.

Before enrolling a subject in the EDC system, registration staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all subjects have signed an appropriate consent form and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization form (if applicable).

For further instructional information, please refer to the *EDC Completion Guidelines.*

15. Statistical Considerations

This section outlines the statistical analysis strategy and methods for the study. If, after the study has begun, but before the conduct of any analysis, 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, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

15.1. Sample Size and Power Calculation

ORR assessed by RECIST 1.1 and iRECIST will be considered as primary efficacy endpoints in each Phase 2a arm and estimated using exact confidence intervals based on the binomial distribution (Clopper-Pearson intervals) from the evaluable subjects for selected arms. All subjects treated on study and 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 in the arm population 4% vs alternative hypothesis 21% 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 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 confidence interval estimates of ORR from each arm is planned to support the primary hypothesis tests.

Enrolment of up to 30 subjects per arm is planned to account for non-evaluable subjects and dropouts. Up to 238 subjects (up to 18 subjects in the 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 would explore the rate of pseudo-progression in NT-I7 plus pembrolizumab assessed by iRECIST 1.1.

In the 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.

15.2. Stratification Factors

No stratification is planned.

15.3. Interim Analyses

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 RECIST 1.1 and

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

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

15.4. Data Monitoring Committee (DMC)

To provide oversight of safety, efficacy, and study conduct, a Data Monitoring Committee (DMC) will be instituted. The voting members of the committee are external to the Sponsor. They must not be involved with the trial in any way (e.g., trial` investigators) and must not have competing interests that could affect their roles with respect to the trial.

The DMC will monitor for subject safety and scientific integrity during the study. The DMC will make a decision for dose escalation or dose-de-escalation in the Phase 1b and determine the RP2D; in Phase 2a and Biomarker Cohort. The DMC will monitor for subject safety and scientific integrity during the study. The DMC will meet to review the safety and efficacy data at the interim analysis for arms I, II, III, IV, and V (i.e., after the 17th evaluable subject enrolled into the arm has had the 1st tumor assessment). At intervals defined by the DMC charter, the DMC will review and evaluate the data on clinical efficacy and safety collected during the study and assesses reports on cumulated SAEs. In addition to the pre-scheduled data reviews and planned safety monitoring, the DMC will convene additional ad hoc meetings to conduct emergency reviews of any event that potentially impacts safety at the request of the sponsor. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC.

15.5. Statistical Analysis Plan Summary

Study Design Overview	An Open-label Phase 1b/2a Study of NT-I7 (efineptakin alfa) in Combination with Pembrolizumab in Subjects with Relapsed/Refractory Advanced Solid Tumors
Analysis Populations	Safety: All-Subjects-as-Treated (ASaT) PK: Per-Protocol (PP) Efficacy: All evaluable per arm, a subset may be repeated on All-Subjects-as-Treated (ASaT).

	Descriptive analysis will be performed at the end of enrollment for Arms IVa and Va.
Primary Endpoint(s)	**Phase 1b:** • Incidence, nature, and severity of adverse events graded according to NCI CTCAE v5.0 • Incidence and nature of DLTs • Potential correlation of dose levels with safety and efficacy parameters **Phase 2a:** • Objective Response Rate (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:** • To assess a potential correlation between tumor infiltrating lymphocytes (TILs) and clinical benefits in subjects with CPI-naïve R/R OC.
Secondary Endpoints	**Phase 1b/2a:** • Duration of objective response (DOR) for 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. • Disease Control Rate (DCR) for each individual arm, defined as proportion of subjects with a best overall response of CR, PR or stable disease (SD), per RECIST 1.1 as determined by the investigator. • Progression Free Survival (PFS) for each individual arm, defined as the time from the first study treatment (Cycle 1, Day 1) to the first occurrence of progression or death from any cause, whichever occurs first, per RECIST 1.1 as determined by the investigator. • Overall survival (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: • To assess the safety and tolerability of NT-I7 in combination with pembrolizumab in subjects with CPI-naïve R/R OC
Statistical Methods for Efficacy Analysis	Primary: ORR will be considered a primary efficacy endpoint and estimated using exact confidence intervals based on the binomial distribution (Clopper-Pearson intervals). A test from the Simon minimax design for null hypothesis ORR proportion in the arm population 4% vs alternative hypothesis 21% will be conducted in each arm at 1-sided alpha = 0.025 and the p-value reported. Arms I, II, III, IV, and V for the Phase 2a study stage will follow the Simon's two-stage minimax design in each arm and has 5 arms. 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 for a total of 25 evaluable subjects/arm. Exact 95% binomial Clopper-Pearson confidence interval estimates of ORR for arms I, II, III, IV, and V are planned to support the primary hypothesis tests. Enrolment of up to 30 subjects per arm is planned to account for non-evaluable subjects and dropouts. Approximately 210 subjects are planned for the Phase 2a study stage. ***Note:*** *In addition to the primary analyses on the population of evaluable subjects for the primary endpoint, exploratory analyses will also be presented on the population of all subjects enrolled and treated on study.* Secondary: • Duration of response (DoR) for the responders in each individual arm, is 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 as determined by the investigator. DoR will be assessed statistically via Kaplan-Meier methods and presented descriptively for the responders. Comparative assessments are not planned on this endpoint. • Disease Control Rate (DCR) for each individual arm, is defined as proportion of subjects with a best overall response of CR, PR or SD, per RECIST 1.1 as determined by the investigator. DCR will be assessed statistically via Fisher Exact tests supported by Clopper-Pearson confidence intervals; all analyses will be interpreted descriptively. Comparative assessments are not planned on this endpoint. • Progression Free Survival (PFS) for each individual arm, is defined as the time from the first study treatment (Cycle 1, Day 1) to the first occurrence of progression or death from any cause,

	whichever occurs first, per RECIST 1.1 as determined by the investigator. PFS will be assessed statistically via Kaplan-Meier methods and presented descriptively for all treated patients in each study arm; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively. Comparative assessments are not planned on this endpoint. • Overall survival (OS) for each individual arm, is defined as the time from first study treatment (Cycle 1, Day 1) to death from any cause. OS will be assessed statistically similarly to PFS (above). • Incidence of anti-drug antibody (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. Additional details are provided in Table 1.
Treatment Assignment	This is not a randomized study.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.
Interim Analyses	For Phase 2a, Arms I, II, III, IV, and V, an interim analysis for futility is included, per the Simon minimax design. An interim analysis will not be performed for Arms IVa, Va, and the Biomarker Cohort Ovarian Cancer. An interim analysis for Phase 1b will be performed.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	Up to 238 subjects (up to 18 subjects in the Phase 1b, up to 210 subjects in the Phase 2a and up to 10 subjects in the Biomarker Cohort) are planned to be enrolled in the study. 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, for 4% vs 21% ORR, at 1-sided alpha = 0.025, as well as approximately 25 evaluable subjects per arms for 95% exact binomial Clopper-Pearson confidence intervals for ORR from the design (per arm).

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17. Abbreviations

ADA	Anti-Drug Antibody
AEs	Adverse Events
AESI	Adverse Event of Special Interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine Amino Transferase
AML	Acute Myelocytic Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASCO-CAP	American Society of Clinical Oncology – College of American Pathologists
AST	Aspartate Amino Transferase
BCG	Bacillus Calmette–Guérin
BICR	Blinded Independent Central Review
BRAF	Proto-oncogene B-Raf
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD	Cluster of Differentiation
CDASH	Clinical Data Acquisition Standards Harmonization
CFR	Code of Federal Regulation
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CISH	Chromogenic in situ hybridization
CNS	Central Nervous System
CPI	Check Point Inhibitor
CR	Complete Response
CRC	Colorectal Cancer
CrCl	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTEP	Cancer Therapy Evaluation Program
CxDx	Cycle x Day x
D1	Day 1
DCR	Disease Control Rate
DILI	Drug-Induced Liver Injury
DL	Dose Level
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
dMMR	deficient Mismatch Repair
DOR	Duration of Response
ECI	Events of Clinical Interest

ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
EKG	Electrocardiogram
EOT	End of Treatment
ER	Estrogen Receptor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed, paraffin embedded
FISH	Fluorescence in situ hybridization
FT3/FT4	free Triiodothyronine/ free Thyroxine
FU	Follow Up
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
hyFC	hybrid Fc
ICF	Informed Consent Form
ICH	International Council for Harmonization
iCPD	iRECIST Confirmed Progressive Disease
iCR	iRECIST Complete Response
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IM	Intramuscular
IME	Important Medical Events
IND/IDE	Investigational New Drug Application/Investigational Device Exemption
INR	International Normalized Ratio
iPD	iRECIST Progressive Disease
iPR	iRECIST Partial Response
IRB	Institutional Review Board
iRC	Immune-Related Response Criteria
iRECIST	modified Response Evaluation Criteria in Solid Tumors
iSD	iRECIST Stable Disease
ITT	Intent-To-Treat
iUPD	iRECIST Unconfirmed Progressive Disease
IV	Intravenous
LDH	Lactate Dehydrogenase
LLN/ULN	Lower Limit of Normal/Upper Limit of Normal
mAb	Monoclonal Antibody
MDS	Myelodysplastic Syndrome
MED	Maximum Effective Dose

MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability High
MSS-CRC	Microsatellite Stable Colorectal Cancer
MTD	Maximum Tolerated Dose
Nab	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NIT	NeoImmuneTech, Inc.
NKT	Natural Killer-T cells
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-small Cell Lung Cancer
NT-I7	rh-IL-7-hyFc ka GX-I7
OC	Ovarian Cancer
ORR	Objective Response Rate
OS	Overall Survival
PC	Pancreatic Cancer
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PD	Progressive Disease
PD-1/PD-L1	Programmed cell death protein 1/Programmed cell death protein - Ligand 1
PFS	Progression Free Survival
Ph. EUR	European Pharmacopeia
PI	Principal Investigator
PK	Pharmacokinetics
pMMR	proficient Mismatch Repair
PR	Partial Response
PR	Progesterone Receptor
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QTc	Corrected QT interval
R/R	Relapsed/Refractory
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	ROS Proto-Oncogene 1
RP2D	Recommended Phase 2 Dose
RP-HPLC	Reverse-Phase High-Performance Liquid Chromatography
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease
SE-UHPLC	Size-Exclusion Ultra-High-Performance Liquid Chromatography
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvate Transaminase
SOC	System Organ Class

T1DM	Type 1 Diabetes Mellitus
TBL	Total bilirubin level
TEAE	Treatment Emergent Adverse Event
TIL	Tumor-infiltrating lymphocyte
TKI	Tyrosine Kinase Inhibitor
TNBC	Triple Negative Breast Cancer
TNF	Tumor Necrosis Factor
TSH	Thyroid Stimulating Hormone
Tx	Treatment
VOP	Verification of Progression
WBC	White Blood Cells

Appendix A – Assessment of Disease

RECIST 1.1 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). RECIST 1.1 references a maximum of 5 target lesions in total, and 2 per organ. (87)

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 will be used by the Investigator to assess tumor response and progression and make treatment decisions. When clinically stable, subjects may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Table 6. iRECIST reflects that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

- If subject is clinically stable, continue study intervention per protocol
    - Perform scans 4 to 8 weeks after RECIST 1.1 progression
    - Continue investigator assessment per iRECIST
- If the subject 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 (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

Any subject deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the subject should continue to receive study treatment. Regardless of the subject is on treatment or off treatment, the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

If a subject has confirmed radiographic progression (iCPD) as defined in Table 6, study treatment should be discontinued; however, if the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following 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 Table 6.

A description of the adaptations and iRECIST process is provided in the latter half of Appendix A – Assessment of Disease, with additional details in the iRECIST publication1. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart in Figure 5.

Figure 5: Imaging and treatment for clinically stable subjects treated with NT-I7+pembrolizumab after first radiologic evidence of PD assessed by the investigator.

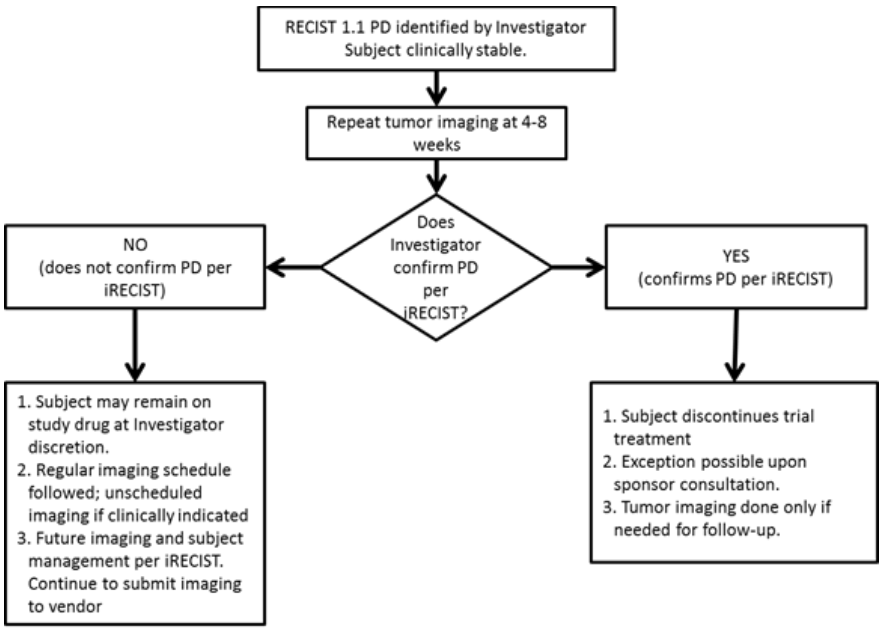

Table 6: Imaging and treatment after first radiologic evidence of progressive disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.; VOP=verification of progression

RECIST 1.1 and iRECIST

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 subjects who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a subject on study treatment until repeat imaging is obtained (using iRECIST for subject management (see Table 6 and Figure 5**).** This decision by the Investigator should be based on the subject's overall clinical condition.
Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

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 Imaging

On the confirmatory imaging, the subject 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 PD 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 PD threshold (by RECIST 1.1)

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.

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 PD 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 pseudo-progression, 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 Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.
Note: If a subject has confirmed radiographic progression (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following 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 **13.**

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- 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 Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), 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 a confirmatory factor causes iCPD.

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

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella Vries GE and RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152. doi: 10.1016/S1470-2045(17)30074-8