NEOIMMUNETECH

A multicenter, open-label, single-arm Phase II study to evaluate anti-tumor efficacy and safety of NT-I7 (efineptakin alfa) in combination with atezolizumab in subjects with previously untreated, PD-L1-expressing, locally advanced or metastatic Non-Small Cell Lung Cancer

Protocol Number:	NIT-119
Version Number:	Version 3.0
Version Date:	15-NOV-2022
Investigational Products:	NT-I7 (also known as efineptakin alfa, rhIL-7-hyFc) Atezolizumab
Abbreviated Title:	NT-I7 (efineptakin alfa) in Combination with Atezolizumab in previously untreated, PD-L1-expressing, locally advanced or metastatic Non-Small Cell Lung Cancer
Study Phase:	Phase II
IND Number:	**152506**
IND Sponsor:	NeoImmuneTech, Inc. 2400 Research Blvd, Suite 250 Rockville, MD 20850 NIT119@neoimmunetech.com www.neoimmunetech.com

Confidential Statement

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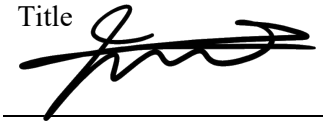
Sponsor Signatory

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

Byung Ha Lee, PhD
Sponsor (print name)

SVP & CSO
Title



Sponsor (signature)

11/16/2022
Date (dd-mm-yyyy)

Investigator Signature Page

Protocol Title: A multicenter, open-label, single-arm Phase II study to evaluate anti-tumor efficacy and safety of NT-I7 (efineptakin alfa) in combination with atezolizumab in subjects with previously untreated, PD-L1-expressing, locally advanced or metastatic Non-Small Cell Lung Cancer
Protocol No.: NIT-119
Version: v3.0, dated 15-NOV-2022

This protocol is a confidential communication of NeoImmuneTech. I have read this protocol in its entirety and agree to participate in and comply with the procedures, as detailed herein for the conduct of this clinical trial. I also agree to comply with the applicable Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonization (ICH), any applicable national and local laws and regulations, and Institutional Review Board (IRB) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.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 NIT119@neoimmunetech.com

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

Signature of Investigator: _____ Date: _____
(dd-mmm-yyyy)

Printed Name: _____

Investigator Title: _____

Site Number:

Name/Address of Center: _____

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Document History

Version	Date of Issue	Summary of Changes
Original Protocol v1.0	03-SEP-2020	Not applicable
Protocol v2.0	05-OCT-2020	Amendment #1 • Study population has been modified from all comers in subjects with Stage IV treatment naïve NSCLC to PD-L1 TPS≥1% subjects with previously untreated, locally advanced or metastatic NSCLC per FDA recommendation. • PK samples will be collected for all subjects who have been administered NT-I7 per FDA recommendation. • Immunogenicity samples will be collected for all subjects who have been administered NT-I7 per FDA recommendation. • Provided immunogenicity sample collection timepoints ie. The first 3 cycles, every other cycle from cycle 3 up to 9 and every 4 cycles after cycle 9, at end of the treatment and at safety follow-up per FDA recommendation. • Study rationale and statistical considerations have been modified per the change of the study population. • Inclusion/Exclusion criteria have been modified to reflect the change of the study population. • Add eligibility criteria for HIV subjects per FDA recommendation. • Provided Cockcroft-Gault formula for creatine clearance calculation per FDA recommendation. • Added additional timepoints for monitoring safety ECG per FDA recommendation. • Provided dose modification guidelines for NT-I7 per FDA recommendation.
Protocol v3.0	15-NOV-2022	Amendment #2 • Added all existing tables to Table of Tables, and updated all Tables of Contents/Figures/Tables for new additions.

		• Addition of iRECIST to primary and secondary objectives
		• Updated schema to include defined values of X and Y, as well as to specify that subject numbers are for evaluable subjects
		• Updated treatment schema to include C4D1 tumor biopsy as well as language around iRECIST
		• Revised duration of relevant systemic exposure from 5 months to 150 days with regard to contraception and pregnancy.
		• Removed option for local lab testing for PD-L1 in Inclusion 4 and throughout the protocol
		• Corrected formatting in Inclusion Criteria #12 (formerly, the units were appearing as boxes)
		• Final Safety Follow up visit changed from 100 days to 90 days
		• Expected duration for accrual of patients updated from 10 months to 24 months
		• Updated duration of participation from 15 months to 27 months to reflect 35 cycles allowed for treatment
		• Updated language to reflect studies that have been completed since the last protocol amendment
		• Deleted information from GX-I7-CA-003 that is already present in the IB, retaining critical safety information
		• Section 4: Removed possibly confusing language around protocol deviations and exemptions
		• Added Section 4.6 about subject screening, with language related to rescreening
		• Section 6.1: Schedule of Assessment table revisions, including:
		  • iRECIST
		  • C2D1 cytokines
		  • C2D8 immunophenotyping and cytokines
		  • Addition of C4D1 peripheral blood sampling and biopsy for exploratory biomarker evaluation
		  • Changed ECG to “as indicated” after screening visit
		  • Addition of serious adverse event assessment from time of consent

		• Removal of EOT peripheral blood sampling for exploratory biomarker evaluation (TCRseq) • Addition of imaging at Safety Follow-Up Day 60 or Day 90 • Addition of imaging every 60-90 days during the first nine months (270 days) of Survival Follow-Up • Removal of language about TCRseq • Updates to footnotes 4, 5, 7, 8, 11, 13, 16, 17, 18, 19, 20, and added footnote 21. • Added mentions of the *NIT-119 General Laboratory Manual, NIT-119 Anatomic Pathology Laboratory Manual, and NIT-119 Flowchart* in appropriate sections. • PK table number updated (previously Table 5, now Table 3) and footnotes updated to clarify timing • Corrected NT-I7 chemical formula • Changed name of section headers for 6.3, 6.3.1., and 6.3.2. and added section header 6.3.3. • Section 6.4.2, Table 3 – changed visit windows to align with Schedule of Assessments. • Clarified language around observation of irAEs (that some were observed in combination therapies, but not monotherapy use) • Section 7.2.2: Updated language to indicate that dose modifications of atezolizumab are not allowed and that additional tests to check for immune etiology of toxicities should be used "when clinically indicated." • Moved section 7.2.2.1 to 7.2.3 for improved readability and logical flow • Clarified language in Table 17 about where to find information on HLH and MAS management (from "in this appendix" to "section 7.2.3.1") • Revised language referring to NIT CMO to NIT "designee" • Revised timeline for dosing delay from 10 weeks to 12 weeks • Section 7.2.3: Updated list of AEs of concern for atezolizumab to include severe cutaneous adverse reactions

		• Section 7.2.3: Updated language for AE management to align with current version of atezolizumab IB. • Section 7.2.3.2, Table 6: Added recommendation to consider withholding atezolizumab for Grade 1 pneumonitis • Section 7.4.1: Revised the scanning interval from every 90 days to every 60-90 days • Section 7.4.2: Language clarified for Discontinuation of Treatment and Withdrawal from Study. • Section 7.5: Included additional language around Study Treatment Beyond Progression, including new table • Sections 7.9 and 7.10: Language clarified for Destruction of Study Drug and Return of Study Drug • Section 8.1: Revised timeframe for receiving live/attenuated vaccines following last dose of study drug from 100 days to 150 days • Section 8.4: Increased the window for recording concomitant medications from 7 days prior to 28 days prior • Section 9: New headings added for clarity, and contact information updated for adverse event reporting • Section 9.2: Trimmed redundant descriptions from expedited reporting requirements table • Section 9.3: Added updated AESIs • Section 10: Changed DSMC to DMC and details surrounding DMC • Added Appendix 3 for iRECIST, and included embedded file for Appendix 2 and inserted table for Appendix 4 (NYHA classifications) rather than stating that these appendices are provided separately • Some language removed and sections combined to eliminate redundancy and improve readability • Table formatting corrected • Added references 42-44.

1. Protocol Summary

1.1. Synopsis

Title	A multicenter, open-label, single-arm Phase II study to evaluate anti-tumor efficacy and safety of NT-I7 (efineptakin alfa) in combination with atezolizumab in subjects with previously untreated, PD-L1-expressing, locally advanced or metastatic Non-Small Cell Lung Cancer
Study Phase	Phase II
Clinical Indication	Locally advanced or metastatic squamous or non-squamous Non-Small Cell Lung Cancer (NSCLC) without prior systemic therapy in the metastatic or locally advanced setting
Study Type	Phase II, multicenter, open-label, single-arm study with the combination of NT-I7 and atezolizumab
Primary Objectives	• To assess the preliminary anti-tumor activity of NT-I7 in combination with atezolizumab, based on Objective Response Rate (ORR) as assessed by Investigators using Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) and immune Response Evaluation Criteria in Solid Tumors (iRECIST), in subjects with PD-L1-expressing (tumor proportion score [TPS] $\geq$ 1%), locally advanced or metastatic squamous or non-squamous NSCLC who have not received prior systemic therapy in the metastatic or locally advanced setting.
Secondary Objectives	• To make further assessment of the anti-tumor activity and efficacy of NT-I7 in combination with atezolizumab 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 the safety and tolerability of NT-I7 in combination with atezolizumab in subjects with PD-L1-expressing, metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC who have not received prior systemic therapy in the metastatic or locally advanced setting.
Exploratory Objectives	• To assess pharmacokinetics (PK) parameters for NT-I7. • To evaluate the immunogenicity of NT-I7. • To explore biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of NT-I7 in combination with atezolizumab. • To explore the relationship(s) between tumor and peripheral blood biomarkers with efficacy, AEs, and/or safety parameters.

Study Design	This is a multicenter, open-label, single-arm Phase II study to evaluate anti-tumor efficacy and safety of NT-I7 in combination with atezolizumab in subjects with PD-L1-expressing (TPS ≥ 1%), metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC who have not received prior systemic therapy in the metastatic or locally advanced setting. Eligible subjects must have measurable disease according to RECIST 1.1. This Phase II study will enroll a minimum of 26 evaluable subjects and a maximum of approximately 76 evaluable subjects; taking into account a non-evaluable rate of approximately 5%, it is planned to enroll up to 83 subjects. The study will follow Simon's 2-stage optimal design (R. Simon, Controlled Clinical Trials 10:1-10 (1989)) with null ORR test rate 21% and alternative ("promising") rate 35%, powered at approximately 80% for 1-sided alpha = 0.05 primary test with 76 evaluable subjects for the final analysis and interim analysis for futility at 26 evaluable subjects. One treatment cycle is defined as 21 days (3 weeks) with 1200 µg/kg NT-I7 administered intramuscularly (IM) once every 6 weeks (Q6W) starting on Cycle 1, and 1200 mg atezolizumab administered intravenously (IV) once every 3 weeks (Q3W) starting on Cycle 1. On days where both drugs are given, atezolizumab will be given prior to NT-I7. The treatment will be continued up to a maximum of 35 cycles (approximately 2 years).
Rationale for Dose Selection	**Rationale for flat dosing of atezolizumab** Atezolizumab (TECENTRIQ®) was approved by FDA for the treatment of NSCLC as single or combination therapy. According to the United States Prescribing Information (US PI), atezolizumab can be given 840 mg IV Q2W, or 1200 mg IV Q3W, or 1680 mg IV Q4W. The atezolizumab dose of 1200 mg IV Q3W was selected for this study for the convenience of the administration since NT-I7 is given 1200 mg IM Q6W.
Study Schema	

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Phase II, multi-center, open label, single arm study

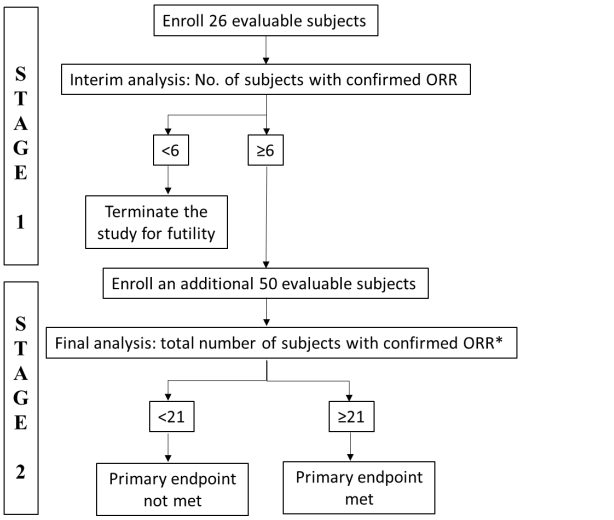
Simon's Two-stage Optimal Design for Testing the Efficacy of NT-I7 plus atezolizumab in 1L NSCLC

Assumptions:
H_0: 0.21, H_1: 0.35
1-sided $\alpha = 0.05$, $\beta = 0.20$

N in Stage I = 26#

Maximum N = 76#

Evaluable subjects



*Including subjects in the previous stage

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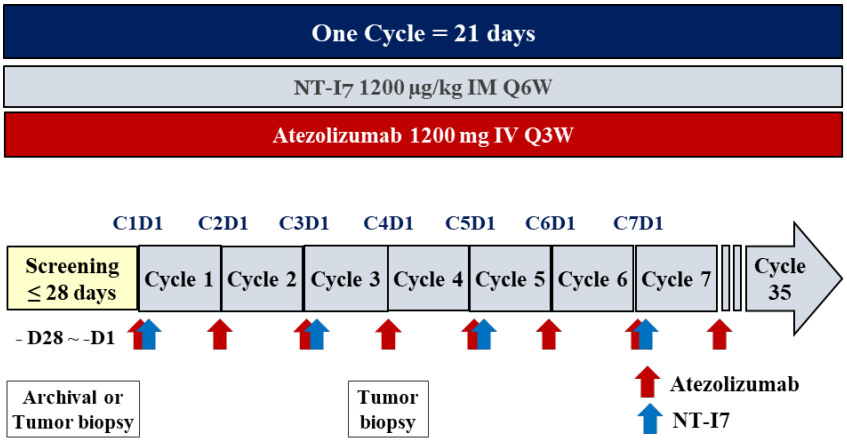

CT/MRI

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 v1.1, a second scan will be scheduled 4-8 weeks later to confirm disease progression by iRECIST. (See Appendix 3 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 before treatment on C4D1.

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<td>Eligibility Requirements</td>
<td>Inclusion Criteria:</td>
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	Subjects must meet all 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. Have histologically or cytologically confirmed metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC, and have not received prior systemic therapy in the metastatic or locally advanced setting. Subjects with locally advanced disease must have Stage III NSCLC and are not candidates for surgical resection or definitive chemoradiation. 4. Tumor PD-L1 expression (TPS≥1%) as determined by 22C3 immunohistochemistry by central lab assay. 5. Have measurable disease defined as at least one lesion that can be accurately measured in at least two dimensions with spiral CT scan. Minimum measurement must be ≥ 10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node. If there is only one target lesion, and it is a non-lymph node, it should have a longest diameter of ≥ 15 mm. 6. Must agree to provide tumor tissue sample, either from a previous surgery or biopsy, or fresh biopsy, prior to the start of treatment. Fresh tumor biopsies should be preferentially obtained from tumor lesions that are safely accessible as determined by the investigator and achieved via non-significant risk procedures. Tumor lesions used for biopsy should not be lesions used as RECIST 1.1 target lesions. Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure. 7. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. 8. Must have a life expectancy of greater than or equal to 12 weeks per assessment from the treating physician. 9. Must have adequate organ function as defined below: • Absolute neutrophil count ≥1,500/μL without granulocyte colony-stimulating factor support • Platelets ≥100,000/μL without transfusion • Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L (Criterion must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks of first dose of study treatment) • Total bilirubin ≤1.5 × institutional upper limit of normal (ULN) OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN • AST(SGOT)/ALT(SGPT) ≤2.5 × ULN (AST and/or ALT ≤5 × ULN for subjects with liver metastasis) • Alkaline phosphatase ≤2.5 × ULN (≤5 x ULN for subjects with documented liver involvement or bone metastases.) • Creatinine ≤1.5 × ULN OR Creatinine clearance (CrCl) ≥30 mL/min for subjects with creatinine levels >1.5 x ULN. CrCl should be calculated per Cockcroft-Gault formula as follows: CrCl=Q x (140-age in years) x weight in kg/72 x serum creatinine in mg/dl; Q=0.85 (Females), Q=1 (Males). • 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. 10. Female subjects are either postmenopausal for at least 1 year, or are surgically

	sterile for at least 6 weeks; if a female subject is of childbearing potential, she must agree to remain abstinent (refrain from heterosexual intercourse) or to follow instructions for dual methods of contraception for the duration of study treatment and for 150 days after the last dose of study treatment (with atezolizumab 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, and 30 days post-treatment. 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 follow instructions for highly effective method(s) of contraception for the duration of study treatment and for 150 days after the last dose of study treatment (with atezolizumab and/or NT-I7). 12. Negative HIV test at screening with the following exception: subjects with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 T cell count > 200/μL, and have an undetectable viral load.
	Exclusion Criteria Subjects meeting <u>any</u> of the following criteria are not eligible for enrollment in the study: 1. Prior systemic anti-cancer therapy for metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC in the metastatic or locally advanced setting. *(Note: Subjects who received prior neo-adjuvant, adjuvant chemotherapy, and/or chemoradiotherapy with curative intent for non-metastatic disease are eligible for the study if the therapy was completed at least 6 months prior to first dose of study treatment.)* 2. NSCLC with EGFR, or ALK, or BRAF or ROS or RET or other genomic tumor aberrations which have available therapy. 3. Pregnant, lactating or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 150 days after the last dose of study treatment. 4. Have 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. 5. Have 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 steroids for at least 14 days prior to study treatment. 6. Have not recovered from AEs (other than alopecia, vitiligo, neuropathy or endocrinopathy managed with replacement therapy) due to agents administered

	6 months prior to first dose of study treatment (i.e., have residual toxicities >Grade 1). 7. Have 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. 8. Have 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. 9. 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 first dose of study treatment. 10. Have autoimmune disease history for the past two 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. (*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.)* 11. Have active and clinically relevant bacterial, fungal, viral, or TB infection, including known Hepatitis A, B, or C (testing not required). 12. Have 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 first dose of study treatment; symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to first dose of study treatment, except controlled atrial fibrillation and paroxysmal supraventricular tachycardia. 13. Have received treatment with systemic immunosuppressive medications (including, but not limited to, prednisone >10 mg/day, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 7 days prior to first dose of study treatment. 14. Have 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).* 15. Have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 16. Have history of 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 treating investigator. 17. Have a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study. 18. Have 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. 19. Have had an allogenic tissue/solid organ transplant or bone marrow transplant.
Sample Size Determination	This Phase II study will enroll a minimum of 26 evaluable subjects and a maximum of approximately 76 evaluable subjects; taking into account a non-evaluable rate of approximately 5%, it is planned to enroll up to 83 subjects. The study will follow Simon's 2-stage optimal design (R. Simon, Controlled Clinical Trials 10:1-10 (1989)) with null ORR test rate 21% and alternative ("promising") rate 35%, powered at approximately 80% for 1-sided alpha = 0.05 primary test with 76 evaluable subjects for the final analysis and interim analysis for futility at 26 evaluable subjects. **Rationale for assuming the null ORR test rate of 21%:** The CITYSCAPE study reported ORR=21% for 1L NSCLC patients with PD-L1 TPS ≥1% who received single-agent atezolizumab (1).
Number of Subjects	Approximately 83 subjects are planned to ensure 76 evaluable subjects for the primary analysis.
Number of Clinical Sites	Approximately 20 clinical research sites are expected 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-specified contact. The active study will end when the last subject completes the 0-day safety follow up visit, approximately 27 months after enrollment.
Estimated Duration of Study	Study accrual is expected to take approximately 24 months and the study is expected to be completed approximately 27 months after the last subject is enrolled.

2. Introduction

2.1. Study Rationale: Atezolizumab in 1L NSCLC

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. The historical first-line standard of care for patients with metastatic NSCLC without oncogenic driver mutations includes platinum-based chemotherapy. However, chemotherapy has provided only a modest benefit, with a limited safety profile, and the median progression-free survival with platinum-based chemotherapy was 4 to 6 months while the median overall survival was 10 to 13 months (2-7). There is an unmet medical need to improve the treatment options for patients with advanced NSCLC in the first-line setting.

Recently the development of immune checkpoint inhibitors (CPIs) has offered a new treatment modality for patients with advanced NSCLC. Under normal physiological condition, immune checkpoint pathways suppress T cell activation and proliferation to prevent excessive immune activation and maintain self-tolerance. Cancer cells may co-opt these inhibitory pathways through overexpression of immune checkpoint proteins on tumor cells. Immune checkpoint inhibitors target these key regulatory pathways and enhance anti-tumor T-cell activity through the inhibition of immune checkpoints such as the programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) receptor (8), thereby improving tumor-specific immune responses. Several CPIs such as atezolizumab, nivolumab and pembrolizumab have been approved for use in NSCLC (9-14).

Atezolizumab is a selective humanized immunoglobulin G1 (IgG1) monoclonal antibody, which binds to PD-L1 on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and inhibits PD-L1 binding to PD-1 or B7.1 on activated T cells. The interruption of the PD-L1/PD-1 releases suppression of immune responses and reactivates antitumor immune responses through increased T-cell priming, expansion and/or effector function. The Fc modification of atezolizumab eliminates antibody-dependent cellular toxicity, thereby preventing depletion of activated effector T-cells (15, 16).

Treatment with atezolizumab has shown clinical benefit in 1L NSCLC as a single agent and in combination with other chemotherapies and targeted agents.

Phase III IMpower150 study evaluated efficacy and safety of combination of atezolizumab with carboplatin and paclitaxel (ABCP) with or without bevacizumab (ACP) and bevacizumab with carboplatin and paclitaxel (BCP) as 1L treatment in patients with stage IV non-squamous NSCLC. Median PFS was significant longer in the ABCP group than in the BCP group (mPFS: 8.3 months vs 6.8 months). Median OS was also significantly improved in the ABCP group than in the BCP group (mOS: 19.2 months vs 14.7 months). The ORR was 63.5% in the ABCP group and 48.0% in the BCP group (17). The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved clinical benefit across all PD-L1 thresholds in all patients and achieved approval as first-line therapy for metastatic non-squamous NSCLC with tumors wild-type for EGFR and ALK (in the US) and metastatic non-squamous NSCLC including patients whose tumors harbor EGFR or ALK aberrations (in the EU).

Phase III IMpower130 study assessed efficacy and safety of atezolizumab with carboplatin plus nab-paclitaxel chemotherapy (ACnP) compared with chemotherapy (CnP) alone as first-line treatment for metastatic non-squamous NSCLC without ALK or EGFR mutations (18). There was a significant improvement in median OS in the atezolizumab plus chemotherapy group vs chemotherapy (18.6 months vs 13.9 months); and median PFS was also significantly prolonged in ACnP than in chemotherapy group (7.0 months vs 5.5 months). The ORR was 49.2% in ACnP vs 31.9% in CnP). Atezolizumab in

combination with carboplatin plus nab-paclitaxel chemotherapy (ACnP) was approved as first-line therapy for metastatic non-squamous NSCLC in the US and EU.

In a phase III IMpower110 study, atezolizumab monotherapy versus platinum-based chemotherapy in PD-L1-selected, chemo-naïve patients with non-squamous or squamous NSCLC showed atezolizumab monotherapy significantly improved median OS by 7.1 months (HR, 0.59; P=0.0106) vs chemotherapy (mOS:20.2 months vs 13.1 months) in the PD-L1 selected patients (≥50% TC or ≥10% IC). The ORR was 30.7% vs 32.1% in atezolizumab vs chemotherapy in the PD-L1 selected patients (TC or IC≥5%) (19). Based on the results from this study, atezolizumab monotherapy achieved approval in the US as first-line treatment for patients with metastatic NSCLC whose tumors have high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) with no EGFR or ALK genomic tumor aberrations.

In a phase II study (CITYSCAPE), co-inhibition of TIGIT and PD-L1 signaling with tiragolumab plus atezolizumab (TA) showed clinical meaningful improvement in overall response rates (ORR) and PFS compared to placebo plus atezolizumab (PA) in chemotherapy-naïve PD-L1+(TPS≥1% by 22C3 IHC pharmDx Dako assay) locally advanced or metastatic NSCLC. ORR was 37% vs 21% in TA vs PA; PFS was 5.5 months vs 3.88 months, HR: 0.58 (1).

Despite these encouraging results, the improvement in ORR with single-agent CPI was often low, and those responders eventually develop resistance to therapy. The combination of CPI with chemotherapy or chemotherapy and anti-angiogenic agent as 1L treatment demonstrated a significant OS benefit for patients with metastatic NSCLC. However, it is only a minority of patients who achieved this transcendent, durable benefit from these combinations. Thus, novel combinatorial strategies that have synergistic or additive mechanism of action to boost the depth and breadth of the response to CPIs and provide further clinical benefits in patients with advanced NSCLC in first-line setting are needed.

2.2. Study Rationale: NT-I7

2.2.1. Background of rhIL-7 and NT-I7

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 (20, 21).

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 (22, 23).

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 signaling. 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 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 asa therapeutic 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, including cancer patients, 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 (TILs), 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 lead 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 no dose-dependent increase in B cells.

2.2.2. Rationale for NT-I7

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 (24). In addition, it has been known that antitumor immunity is attenuated by suppressor cells and regulatory T cells, as well as check points such as programmed death-1 (PD-1), in tumor microenvironment (TME) of esophageal cancer (25). IL-7 has been shown to increase TCR repertoire in subjects by (1) expanding naïve T cell pools (26) and (2) supporting subdominant T cell clones and improving the survival of the CD8 memory pool (27). In addition to reversing lymphopenia, IL-7 has also been shown to enhance the functionality of effector T cells (28) and to antagonize the immunosuppressive effects of Tregs and MDSCs (29). 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.

NT-I7 is a long-acting human IL-7 being developed for use in the treatment of cancer and infectious diseases, where T cell amplification and increased functionality may provide clinical benefit. IL-7 signaling is necessary for thymocyte development and normal thymopoiesis. Beyond its role in development, IL-7 is a homeostatic growth factor for T-cells and is capable of inducing proliferation, maintaining T-cell responsiveness, and preventing and reversing T-cell anergy.

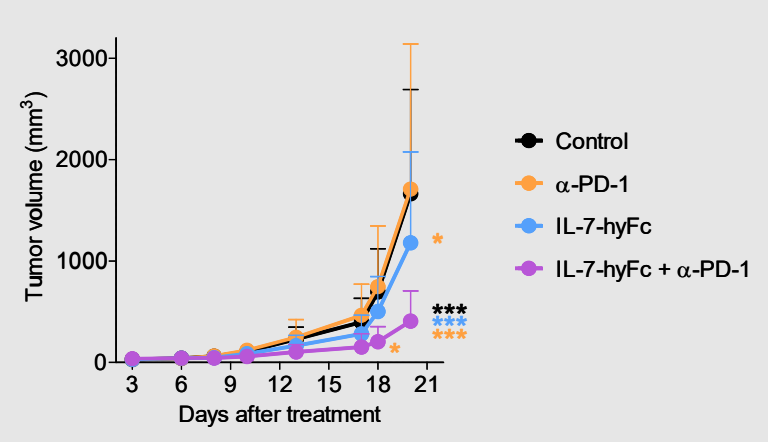
Hence, based on the mechanism of action for NT-I7 and the data obtained from preclinical and clinical studies, adding NT-I7 to a PD-L1 inhibitor, such as atezolizumab, potentially increase the depth and breadth

of the response to single-agent CPI and provide further clinical benefits to PD-L1 selected subjects with metastatic (Stage IV) or locally advanced treatment-naïve NSCLC.

2.2.2.1. 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. With regards to combinations with 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 in 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.

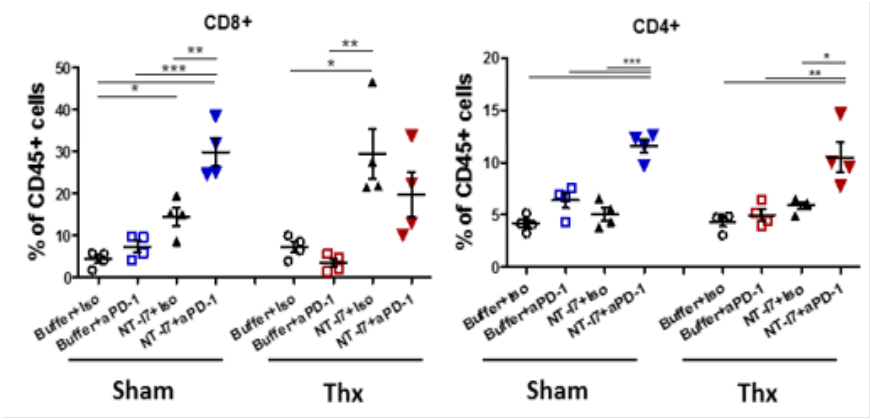
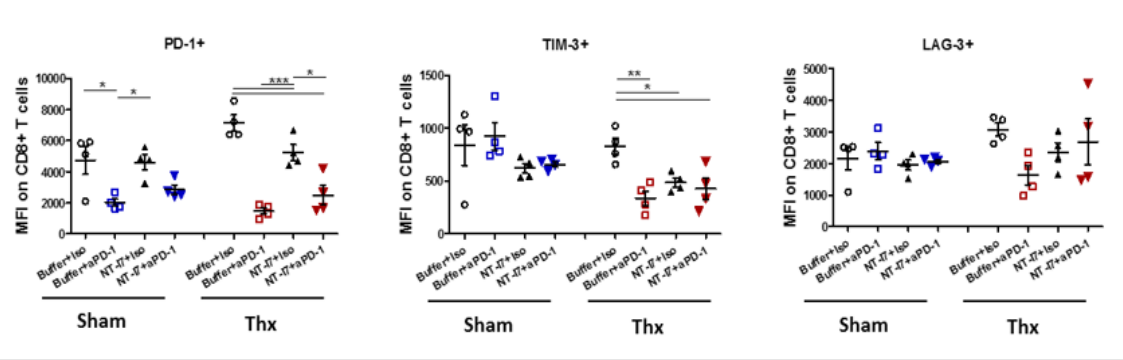
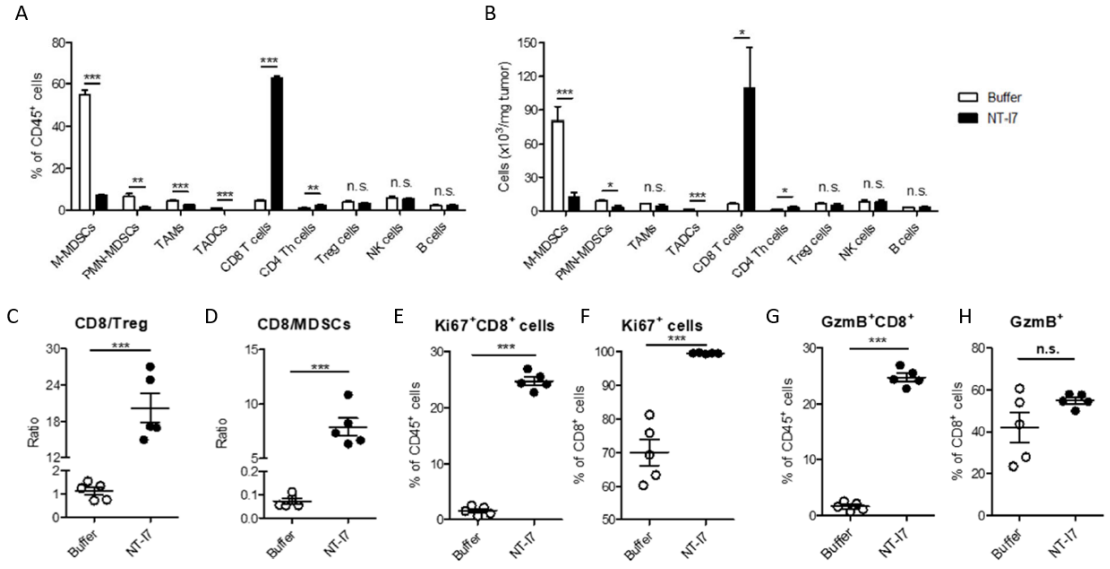


Figure 3: Down-regulation of PD-1 and TIM-3 immune checkpoint expression on CD8+ TILs is correlated with enhanced anti-tumor activity of NT-I7 and anti-PD-1 combination therapy.



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.



Thus, in preclinical tumor models, NT-I7 in combination with anti-PD-1/PD-L1 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.

2.2.2.2. Clinical Studies

Data from the completed study of NT-I7 monotherapy in healthy volunteers (GX-I7-HV-001) in 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 SC administration. In addition, data from the completed study of NT-I7 in combination with pembrolizumab in subjects with relapsed or recurrent metastatic Triple Negative Breast Cancer (mTNBC) showed that NT-I7 in combination with pembrolizumab was well tolerated, and no significant safety findings were reported (GX-I7-CA-006 / KEYNOTE-899).

2.2.2.2.1. 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. A total of 24 subjects received NT-I7: 8 in each of the 3 NT-I7 treatment groups. A total of 6 subjects received matching placebo: 2 corresponding to each of the 3 NT-I7 treatment groups.

NT-I7 was slowly absorbed, particularly after SC administration (time to maximum concentration [T_{max}]: 36 to 42 hours postdose), 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 postdose 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 hours 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.*

2.2.2.2.2. 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 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.

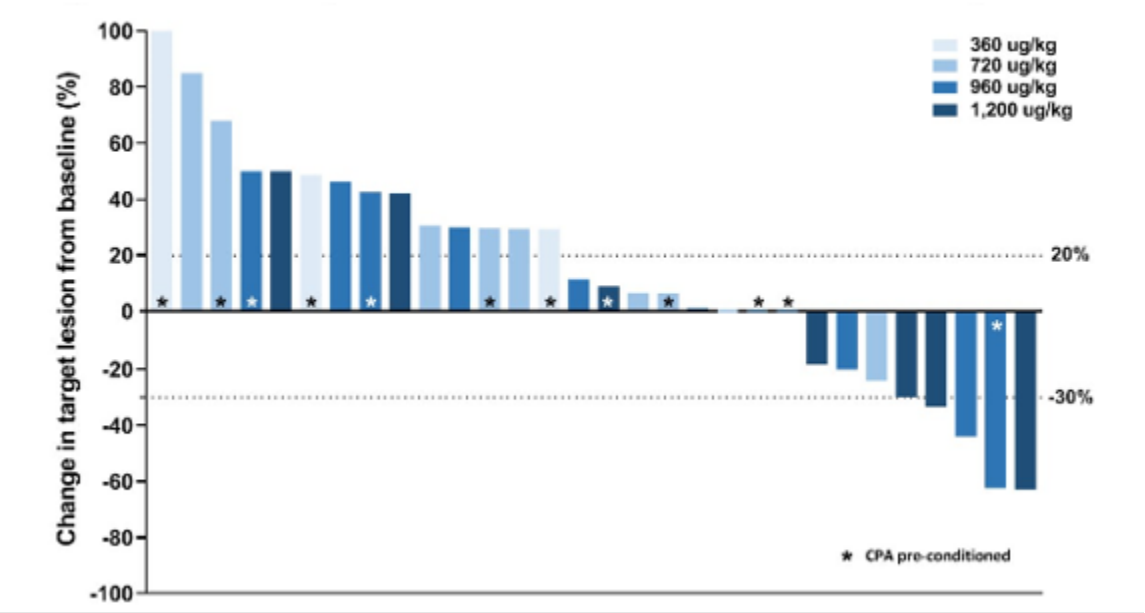
There were 10 AEs of special interest (AESI) as specified in the protocol in 5 subjects. The AESI included cases of potential drug-induced liver injury, conditions suggestive of autoimmune disorders, Grade 2 or higher AEs suggestive of hypersensitivity or immune-mediated reaction, Grade 2 or higher hypoxia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

2.2.2.2.3. KEYNOTE-899 / GX-I7-CA-006

A Phase 1b/2 study of NT-I7 in combination with pembrolizumab in subjects with relapsed or recurrent metastatic Triple Negative Breast Cancer (mTNBC) is being conducted in Korea (Study No. GX-I7-CA-006, also known as KEYNOTE-899). A total of 45 subjects had been enrolled as of April 30, 2020. Thirty patients were available for the assessment of safety and efficacy. Data from the dose escalation phase of the study showed that NT-I7 in combination with pembrolizumab was well tolerated, no Dose Limiting Toxicity (DLT) was observed, and no significant safety findings were reported. The combination treatment significantly increased T cell numbers at NT-I7 doses from 360 µg/kg to 1,200 µg/kg. Disease control rate (DCR) and Objective Response Rate (ORR) tend to increase in a dose-dependent manner by NT-I7 administration. ORR for subjects treated with 1,200 µg/kg of NT-I7 and standard dose of pembrolizumab (200 mg IV Q3W) was 50% (3 Partial Responses in 6 subjects) and, therefore this combination dose is currently being considered as a Recommended Phase 2 Dose (RP2D) candidate for the expansion phase (Figure 5) (30).

Figure 5: Best percentage in target lesion from baseline



Conclusion: Taken together the preclinical data and clinical data of NT-I7, NT-I7 treatment may increase CD4+ and CD8+ T cell responses in cancer patients and provide further clinical benefit to cancer patients in combination with CPI.

2.3. Rationale for Dose and Schedule of Atezolizumab

2.3.1. Rationale for Flat Dosing of Atezolizumab

Atezolizumab (TECENTRIQ®) was approved by FDA for the treatment of NSCLC as single or combination therapy. According to the US PI, atezolizumab can be given 840 mg IV Q2W, or 1200 mg IV Q3W, or 1680 mg IV Q4W. The atezolizumab dose of 1200 mg IV Q3W was selected for this study for the convenience of the administration since NT-I7 is given 1200 mg IM Q6W (14).

3. Objectives and Endpoints

This is a multicenter, open-label, single-arm Phase II study to determine the safety and efficacy of NT-I7 in combination with atezolizumab in subjects with previously untreated, PD-L1-expressing (TPS≥1%), metastatic (Stage IV) or locally advanced NSCLC.

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	
• To assess the preliminary anti-tumor activity of NT-I7 in combination with atezolizumab, based on Objective Response Rate (ORR) as assessed by Investigators using Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) and immune Response Evaluation Criteria in Solid Tumors (iRECIST), in subjects with PD-L1 TPS≥1%, metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC who have not received prior systemic therapy in the metastatic or locally advanced setting.	• Objective Response Rate (ORR), defined as the percentage of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR), per RECIST 1.1 and iRECIST as determined by the investigator.
Secondary Objectives	
• To make further assessment of the anti-tumor activity and efficacy of NT-I7 in combination with atezolizumab based on Duration of Response (DoR), Disease Control Rate (DCR), Progression-Free Survival (PFS), and Overall Survival (OS) by RECIST 1.1 and iRECIST.	• Duration of response (DoR) for the responders 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) 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. • Progression Free Survival (PFS) 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. • Overall survival (OS) defined as the time from first study treatment (Cycle 1, Day 1) to death from any cause.
• To evaluate the safety and tolerability of NT-I7 in combination with atezolizumab in subjects with PD-L1 TPS≥1%, metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC who have not received prior systemic therapy in the metastatic or locally advanced setting.	• Incidence, nature, and severity of adverse events grade according to NCI CTCAE v 5.0
Exploratory Objectives	
• To assess pharmacokinetics (PK) parameters for NT-I7.	• Respective serum concentration of NT-I7 administered at specified timepoints for the following non-compartmental PK parameters: Area under the concentration- time curve (AUC), maximum observed concentration (C_{max}), time to reach C_{max} (T_{max}), clearance, volume of distribution, and terminal half-life ($T_{1/2}$).
• To evaluate the immunogenicity of NT-I7	• Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to baseline.
• To explore biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of NT-I7 in combination with atezolizumab.	• Effect of NT-I7 assessed in tumor tissue and peripheral blood including but not limited to the following: o Tumor biopsy analyses of tumor mutational burden (TMB), tumor-infiltrating immune (TILs), and PD-L1 o Immunophenotyping of circulating PBMCs. • Assessment of cytokines and chemokines as markers of immune modulation.
• To explore the relationship(s) between tumor and peripheral blood biomarkers with efficacy, AEs, and/or safety parameters.	• Correlation of tumor and peripheral blood biomarkers including but not limited to PD-L1 and TMB with ORR, PFS, and OS.

	• Correlation of tumor and peripheral blood biomarkers including but not limited to PD-L1 and TMB with incidence of AEs.

4. Study Population

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.

4.1. Inclusion Criteria

Subjects must meet all 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. Have histologically or cytologically confirmed metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC, and have not received prior systemic therapy in the metastatic or locally advanced setting. Subjects with locally advanced disease must have Stage III NSCLC and are not candidates for surgical resection or definitive chemoradiation.
4. Tumor PD-L1 expression (TPS≥1%) as determined by PD-L1 22C3 immunohistochemistry by central lab assay.
5. Have measurable disease defined as at least one lesion that can be accurately measured in at least two dimensions with spiral CT scan. Minimum measurement must be ≥ 10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node. If there is only one target lesion, and it is a non-lymph node, it should have a longest diameter of ≥ 15 mm.
6. Must agree to provide tumor tissue sample, either from a previous surgery or biopsy (archival in the metastatic setting), or fresh biopsy, prior to the start of treatment. Fresh tumor biopsies should be preferentially obtained from tumor lesions that are safely accessible as determined by the investigator and achieved via non-significant risk procedures. Tumor lesions used for biopsy should not be lesions used as RECIST 1.1 target lesions. Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
8. Must have a life expectancy of greater than or equal to 12 weeks per assessment from the treating physician.
9. Must have adequate organ function as defined below:

    - Absolute neutrophil count ≥1,500/µL without granulocyte colony-stimulating factor support
    - Platelets ≥100,000/µL without transfusion
    - Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L (Criterion must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks of first dose of study treatment)
    - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN) OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
    - AST(SGOT)/ALT(SGPT) ≤2.5 × ULN (AST and/or ALT ≤5 × ULN for subjects with liver metastasis)
    - Alkaline phosphatase ≤2.5 × ULN (≤5 x ULN for subjects with documented liver involvement or bone metastases.)
    - Creatinine ≤1.5 × ULN OR Creatinine clearance (CrCl) ≥30 mL/min for subjects with creatinine levels >1.5 x ULN. CrCl should be calculated per Cockcroft-Gault formula as follows:
      CrCl=Q x (140-age in years) x weight in kg/72 x serum creatinine in mg/dl; Q=0.85 (Females), Q=1 (Males).

- 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.

10. Female subjects are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks; if a female subject is of childbearing potential, she must agree to remain abstinent (refrain from heterosexual intercourse) or to follow instructions for dual methods of contraception for the duration of study treatment and for 150 days after the last dose of study treatment (with atezolizumab 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, and 30 days post-treatment. 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 follow instructions for highly effective method(s) of contraception for the duration of study treatment and for 150 days after the last dose of study treatment (with atezolizumab and/or NT-I7).
12. Negative HIV test at screening with the following exception: subjects with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 T cell count > 200 μL, and have an undetectable viral load.

4.2. **Exclusion Criteria**

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

1. Prior systemic anti-cancer therapy for metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC in the metastatic or locally advanced setting. (*Note: subjects who received prior neo-adjuvant, adjuvant chemotherapy, and/or chemoradiotherapy with curative intent for non-metastatic disease are eligible for the study if the therapy was completed at least 6 months prior to first dose of study treatment.*)
2. NSCLC with EGFR, or ALK, or BRAF or ROS or RET or other genomic tumor aberrations which have available therapy.
3. Pregnant, lactating or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 150 days after the last dose of study treatment.
4. Have 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.
5. Have 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 steroids for at least 14 days prior to study treatment.
6. Have not recovered from AEs (other than alopecia, vitiligo, neuropathy or endocrinopathy managed with replacement therapy) due to agents administered 6 months prior to first dose of study treatment (i.e., have residual toxicities >Grade 1).

7. Have 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.
8. Have 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.
9. 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 first dose of study treatment.
10. Have autoimmune disease history for the past two 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. (*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.)*
11. Have active and clinically relevant bacterial, fungal, viral, or TB infection, including known Hepatitis A, B, or C (testing not required).
12. Have 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 first dose of study treatment; symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to first dose of study treatment, except controlled atrial fibrillation and paroxysmal supraventricular tachycardia.
13. Have received treatment with systemic immunosuppressive medications (including, but not limited to, prednisone >10 mg/day, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 7 days prior to first dose of study treatment.
14. Have 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).*
15. Have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
16. Have history of 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 treating investigator.
17. Have a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.
18. Have 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.
19. Have had an allogenic tissue/solid organ transplant or bone marrow transplant.

4.3. Inclusion of Women and Minorities

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

4.4. Reproductive Status and Contraception

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

Based on its mechanism of action and data from animal studies, atezolizumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of atezolizumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death.

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.

Definition of Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

4.4.1 Contraception Guidance for Female Subjects of Childbearing Potential

Investigators shall inform subjects that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

Female subjects, women of childbearing potential (WOCBP), must adhere to remain abstinent (refrain from heterosexual intercourse) or to follow instructions for one highly effective method of contraception for the duration of study treatment and until the end of relevant systemic exposure, defined as 150 days after the last dose of study treatment. Highly effective methods of contraception are as listed below:

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly.[a]

• Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation.[b] – Oral – Intravaginal – Transdermal
• Progesterone-only hormonal contraception associated with inhibition of ovulation.[b] – Oral – Injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation.[b] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner with documented azoospermia 90 days after procedure *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP subjects chooses to forego complete abstinence
NOTES: [a.] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b.] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c.] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not later contraception effectiveness.

Unacceptable Methods of Contraception
Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

Local laws and regulations may require use of alternative and/or additional contraception methods.

4.4.2 Contraception Guidance for Male Subjects With Partner(s) of Childbearing Potential.

Male subjects with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

• Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

• Male subjects are required to use a condom for study duration and until end of relevant systemic exposure defined as 5 months after the end of study treatment.

• Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 150 days after the end of treatment in the male subject.

• Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 5months after the end of study treatment.

• Refrain from donating sperm for the duration of the study treatment and until 150 days after the end of study treatment.

4.5. Number of Subjects

Up to approximately 83 subjects will be enrolled in this study at approximately 20 centers in the US, including hospitals and freestanding cancer clinics.

4.6. Screening

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 4 – Study Population. Visit requirements are outlined in Section 6 – Study Assessments and Procedures.

Subjects may be re-screened once after initially failing to meet the inclusion/exclusion criteria. A new screening number must be assigned for anyone re-screened. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met.

5. Study Design

This is a multicenter, open-label, single-arm Phase II study to evaluate anti-tumor efficacy and safety of NT-I7 in combination with atezolizumab in subjects with PD-L1-expressing (TPS≥1%), metastatic (Stage IV) or locally advanced squamous or non-squamous NSCLC who have not received prior systemic therapy in the metastatic or locally advanced setting.

Eligible subjects must have measurable disease according to RECIST 1.1. This Phase II study will enroll a minimum of 26 evaluable subjects and a maximum of approximately 76 evaluable subjects, taking into account a non-evaluable rate of approximately 5%, it is planned to enroll up to 83 subjects.

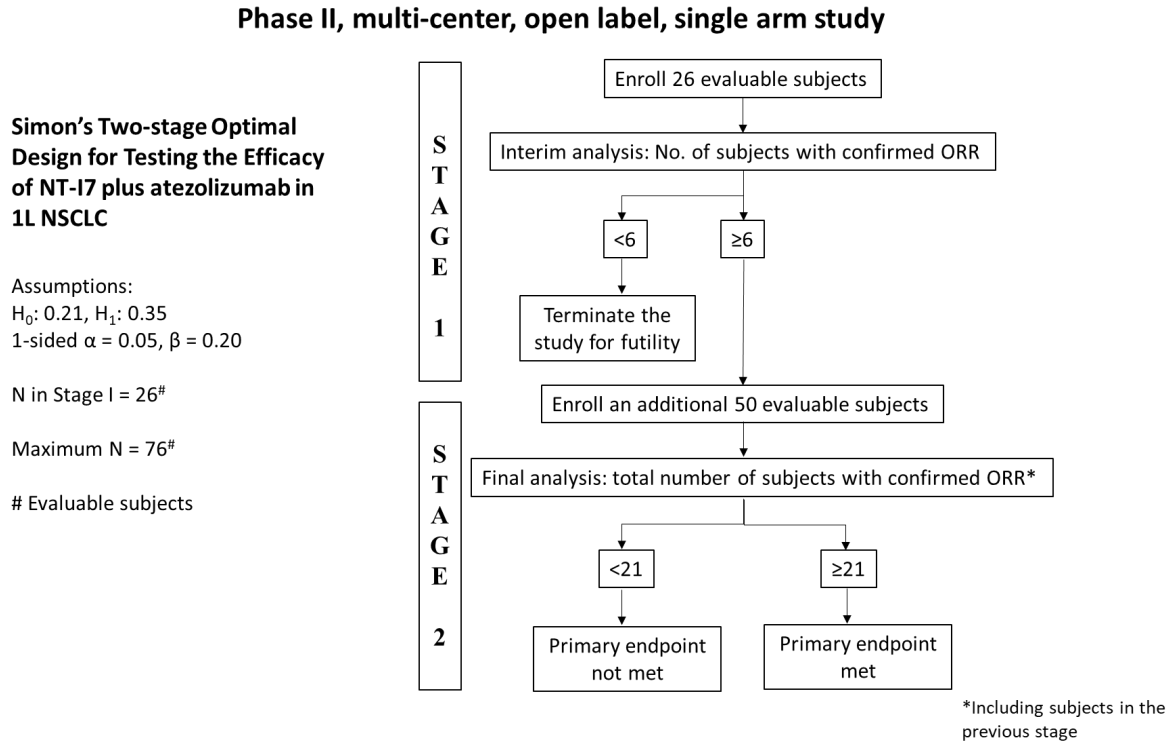
The study will follow Simon's 2-stage optimal design (31) with null ORR test rate 21% and alternative ("promising") rate 35%, powered at approximately 80% for 1-sided alpha = 0.05 primary test with 76 evaluable subjects for the final analysis and interim analysis for futility at 26 evaluable subjects.

One treatment cycle is defined as 21 days (3 weeks) with 1200 µg/kg NT-I7 administered intramuscularly (IM) once every 6 weeks (Q6W) starting on Cycle 1, and 1200 mg atezolizumab administered intravenously (IV) once every 3 weeks (Q3W) starting on Cycle 1. On days where both drugs are given, atezolizumab will be given prior to NT-I7. The treatment will be continued up to a maximum of 35 cycles (approximately 2 years).

5.1. Study Design Schema

The study design schema is presented in **Figure 6.**

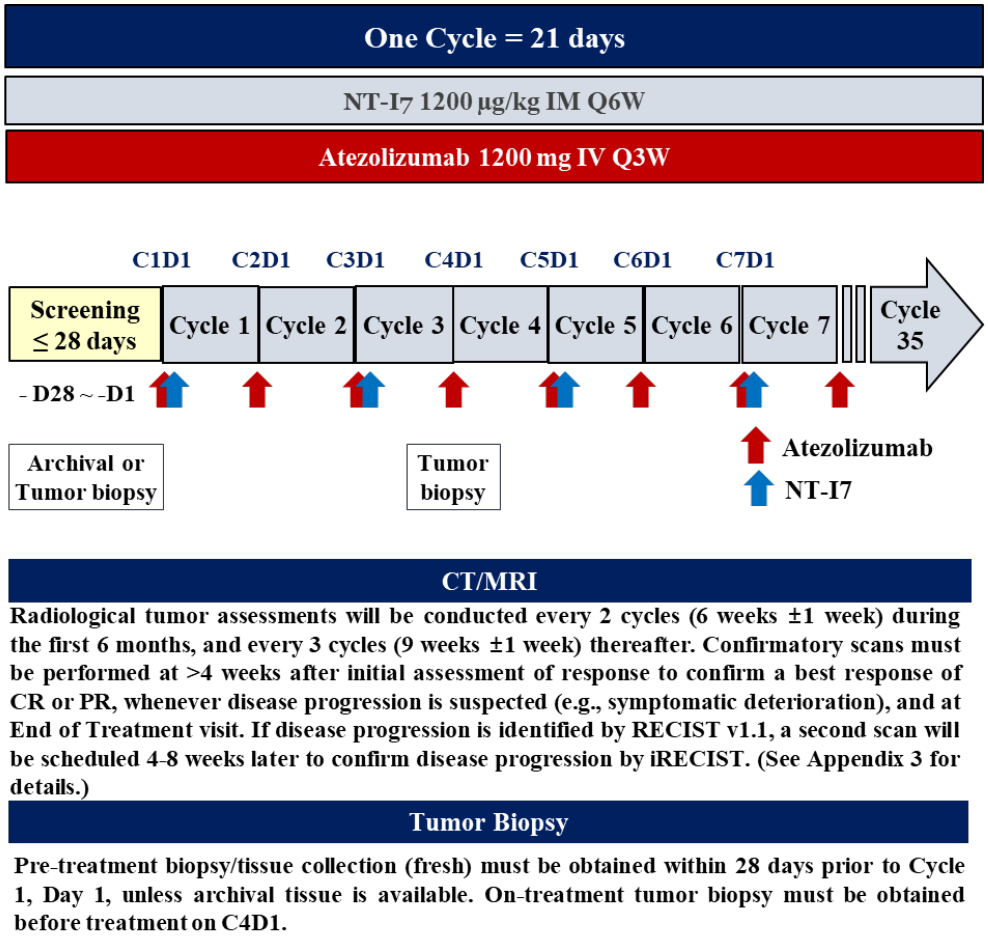
Figure 6: Study Design Schema



5.2. Treatment Schema

The treatment schema is presented in **Figure 7**.

Figure 7: Treatment Schema



5.3. Sponsor Study Stopping Rules

NeoImmuneTech may terminate this study after informing investigators at any time. Investigators will be notified by NeoImmuneTech (or designee) if the study is placed on hold, completed, or closed.

Conditions that may warrant termination of the study include, but are not limited to the following:

- The discovery of unexpected, serious, or unacceptable risk to the subjects in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of product.

6. Study Assessments and Procedures

Prior to any procedures and assessments, a copy of the signed and dated ICF will be provided to the subject. The original ICF will be retained by the Investigator. 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.

6.1. Schedule of Assessments

Table 2: Study Schedule of Assessment

Treatment (Tx) Cycle/ Visit*	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Subsequent Cycles	End of Tx (EOT)[19]	Post Tx Follow Up			
											Safety FU[20]			Survival FU[21]
Scheduling Window	Within 28 days	Day 1	Day 8 ±2 days	Day 1 ±2 days	Day 8 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 1 ±2 days		30 days after last dose ±7 days	60 days after last dose ± 7 days	90 days after last dose ±7 days	Every 90 days after FU Visit 3 ±7 days
Atezolizumab[1]		X		X		X	X	X	X					
NT-I7[2]		X				X		X	X (odd cycles only)					
Informed consent[3]	X													
Inclusion/Exclusion Criteria[4]	X													
Demographics	X													
Medical history	X													
Safety Assessments**														
Prior and concomitant medications[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[6]	X	X		X		X	X	X	X	X	X	X	X	
ECOG Performance Status	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			
Height	X													
Weight	X	X		X		X	X	X	X	X	X			
Adverse Events Assessments[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[9]	X	X (as indicated)												
CBC w/diff, platelets[10]	X	X	X	X		X	X	X	X	X	X			
Serum chemistry[11]	X	X	X	X		X	X	X	X	X	X			
PT/INR and aPTT	X	X								X				
Thyroid Function[12]	X	X				X		X	Odd cycles	X				
Serum or Urine Pregnancy Test[13]	X	X		X		X	X	X	X	X	X			

Treatment (Tx) Cycle/ Visit*	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Subsequent Cycles	End of Tx (EOT)[19]	Post Tx Follow Up			
											Safety FU[20]			Survival FU[21]
Scheduling Window	Within 28 days	Day 1	Day 8 ±2 days	Day 1 ±2 days	Day 8 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 1 ±2 days	Day 1 ±2 days		30 days after last dose ±7 days	60 days after last dose ± 7 days	90 days after last dose ±7 days	Every 90 days after FU Visit 3 ±7 days
Urine Analysis[14]	X	X		X		X	X	X	X	X				
Survival Status[15]														X
Efficacy Measurements														
Tumor evaluation (CT/MRI)[16]	X	RECIST 1.1 and iRECIST algorithm: Every 6 weeks (± 1 week) for the first 6 months, then every 9 weeks (± 1 week) until disease progression or study discontinuation.								X		X[20]	X[20]	X[16]
Tumor Biopsies/Archival Tissue Collection														
Archived Tumor Tissue or Fresh Tumor Biopsy[17]	X						X							
Correlative Studies**														
Immunophenotyping[18]		X	X	X	X	X	X			X				
Cytokines[18]		X	X	X	X	X	X			X				
Blood samples for biomarker analysis[18]		X					X							
Pharmacokinetics	Refer to Table 3, Section 6.4 for PK sampling													
Immunogenicity	Refer to Table 3, Section 6.4 for ADA sampling													

* One treatment cycle is defined as 21 days (3 weeks) with NT-I7 administered IM on Day 1 of every other cycle (Q6W) starting in Cycle 1, and atezolizumab 1200 mg administered IV on Day 1 of every cycle (Q3W).

** Unless otherwise specified, all clinic procedures and sample collection are to be done prior to NT-I7 and/or atezolizumab dosing.

[1]Atezolizumab: Dose as assigned; once every 3 weeks, starting Cycle 1, Day 1.

[2]NT-I7: Dose as assigned; once every 6 weeks, starting Cycle 1, Day 1. NT-I7 must be dosed 45 (±15) minutes after atezolizumab on days where concurrent administration is planned.

[3]Written consent must be obtained prior to performing any protocol specified procedure. A copy of the signed and dated ICF will be provided to the subject. The original ICF will be retained by the Investigator.

[4]All inclusion/exclusion criteria should be assessed during screening period, prior to first dose.

[5] Prior medications – Record all medications (prescription and over-the-counter [OTC]) taken within 28 days (4 weeks) prior to the first dose of study treatment). Concomitant medications – Enter all medications (prescription and OTC) taken after first dose of study treatment on Cycle 1, Day 1 through the Safety Follow-up visit Day 90 (± 7 days) after the last dose.

[6] 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.

[7] Vital signs consist of blood pressure, heart rate, respiratory rate, and temperature. See Sections 7.1.1.2 (NT-I7) and 7.1.2 (Atezolizumab) for vital sign collection requirements on treatment days.

[8] All AEs meeting serious criteria, from the time of consent through 90 days following cessation of study treatment. See Section 9 for additional details on reporting of AEs.

[9]12-lead duplicate ECGs (+/- 5 minutes apart) will be obtained at Screening. If clinically indicated, additional ECGs may be obtained during the study.

[10] 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.

[11]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).

[12]At screening, thyroid function testing is to include TSH, free T3 and free T4. At subsequent timepoints, thyroid function testing consists of TSH only. However, if the TSH is abnormal, reflexive testing of free T3 and free T4 are to be performed.

[13]Serum pregnancy test to be performed at the screening visit for all females except those surgically sterile for at least 6 weeks or postmenopausal for at least 1 year. Subsequent tests to be performed on urine samples. If positive, then test to be repeated with serum pregnancy test.

[14]Urinalysis (a urine dipstick may be used) at screening and Day 1 of each cycle.

[15]Survival status and additional subsequent cancer therapy details (if applicable) such as regimen, setting of the regimen, start date and end date of the regimen, best response to the regimen and date of progression after the subsequent therapy will be collected.

[16]Baseline CT/MRI tumor imaging must be performed within 28 days (4 weeks) prior to first dose. 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. On-study radiological tumor assessments will begin at week 6 post first dose date (± 7 days) and be performed every 2 cycles (6 weeks ± 1 week) until 6 months, at which time scans will be performed every 3 cycles (9 weeks ± 1 week). (Note: Subjects do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks after the previous scan). Refer to section 6.3, Appendix 2 (RECIST 1.1) and Appendix 3 (iRECIST) for additional guidance.

[17]Pre-treatment tumor tissue sample should be obtained either from freshly collected biopsy during screening or from previous surgery or biopsy and prior to the start of treatment in this study. On-treatment tumor tissue sample should be freshly collected from all available patients at the Cycle 4 visit. For newly collected biopsies (screening and Cycle 4), fresh tumor biopsies or formalin-fixed paraffin embedded tumor tissue blocks should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and collected via non-significant risk procedures. Tumor lesions used for biopsy should not be lesions used as RECIST 1.1 target lesions. For archival tissue a minimum of 25 unstained tumor tissue sections are acceptable. Submission of fewer than 25 unstained slides may be acceptable in some circumstances following discussion with the Study Medical Monitor.

[18]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, cytokines, and other biomarker analysis. Additional information on handling and shipping are provided in the *NIT-119 Generic Laboratory Manual*

[19]End of Treatment (EOT) visit will occur approximately anytime within 7 days after disease progression determination or treatment discontinuation, or immediately before initiation of any other cancer therapy whichever occurs first.

[20]Safety Follow-Up visits will be performed in clinic at 30 days (± 7 days), 60 days (± 7 days), and 90 days (± 7 days) after the last dose. Tumor imaging can be performed at Safety Follow-Up day 60 (± 7 days) or Day 90 (± 7 days).

[21]Survival Follow-Up Visits will be done via documented telephone calls every 90 days (± 7 days) from Safety Follow-Up Day 90, to assess the subject's status 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.
Survival Follow-Up CT/MRI tumor imaging will be performed every 60-90 days for the first nine months (270 days).

6.2. Safety Assessments

Schedule of Assessments shows all procedures to be conducted at the screening visit, on-treatment, end of treatment, and follow-up visits. Refer to Table 2**.**

Whenever vital signs (heart rate, respiratory rate, blood pressure, and temperature), 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.

6.3. Tumor Imaging and Assessment of Disease

Study evaluations (tumor assessments) will take place in accordance with Table 2. Measurement of tumor response by a trained radiologist/nuclear medicine physician at each clinical site will be chronicled and reported. The images may be collected for review for a central review, at a later time, at the discretion of the Sponsor.

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). Contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a subject throughout the duration of 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. If brain imaging is performed to document the stability of existing metastases, MRI should be used, if possible. However, CT imaging of brain is acceptable if MRI is medically contraindicated.

6.3.1. Initial Tumor Imaging and Assessment

Initial tumor imaging at Screening must be performed within 28 days (4 weeks) prior to the date of study treatment. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. 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.

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.

6.3.2. 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 2 cycles (6 weeks ± 1 week) for the first 6 months and every 9 weeks (±1 week), or more frequently if clinically indicated, until disease progression or treatment discontinuation. 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.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response will be assessed by the Investigator using RECIST 1.1 and iRECIST.

Per RECIST 1.1, 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, 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 3. 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 3.

6.3.3. 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.

or subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging.

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 every 60-90 days (± 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.

For efficacy assessments, every effort will be made to collect survival data on all subjects including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

6.4. Correlative Studies and Biomarker Assessments

To explore the biological mechanisms, pharmacodynamic (PD) effects, and prognostic/predictive and treatment-associated determinants of response of the investigational treatment regimen, tumor tissues (archival or biopsies) and peripheral blood samples will be utilized. Pre-treatment sampling is mandatory for all study subjects for retrospective analysis. Pre-treatment tumor tissue sample (archival in the metastatic setting; or fresh tumor biopsy prior to study treatment) will be collected at screening for all study subjects for determination of PD-L1 status (central lab) and TMB by local or a study-designated central lab. On-treatment biopsy at C4D1 and on-treatment peripheral blood at different timepoints will be obtained for exploratory biomarker evaluations.

Tumor Tissue Specimens

Fresh biopsy must be obtained within 28 days (4 weeks) prior to initiation of study drugs to establish baseline characteristics of the tumor. Freshly obtained biopsy sample should be collected using core needle procedure; alternative procedures (e.g., cup, punch excisional, incisional) that are expected to produce a tissue sample greater than or equal to core biopsy, may also be acceptable.

Archival FFPE tumor tissue may be used in place of a fresh biopsy if the archival tissue was obtained in the metastatic setting and prior to initiation of the study treatment. If submitting archival tissue, FFPE tumor tissue blocks or a minimum of 25 unstained tumor tissue FFPE section of 5-micron thickness are acceptable. Submission of fewer than 25 unstained slides may be acceptable in some circumstances following discussion with the Study Medical Monitor. A fresh tumor biopsy will be collected at C4D1. For detailed instructions on biopsy sample processing (collection, handling, and shipping), please refer to the *NIT-119* Anatomic Pathology *Laboratory Manual* and *NIT-119 Flowchart.*

Exploratory biomarker analyses may include, but not limited to, quantitation and characterization of PD-L1 expression, tumor-infiltrating immune cells, TMB and other molecular assessments (e.g., TCR repertoire diversity analysis, gene expression profiling, etc.). For detailed instructions on biopsy sample processing (collection, handling, and shipping), please refer to the *NIT-119 Anatomic Pathology Laboratory Manual and NIT-119 Flowchart*.

6.4.1. Planned Peripheral Blood Biomarker Analyses

Study subjects are required to provide peripheral blood samples for exploratory biomarker evaluations throughout their study participation as summarized in the Schedule of Assessments (Table 3). For detailed instructions on peripheral blood research sample processing (collection, handling, and shipping), please refer to the *NIT-119 Generic Laboratory Manual*.

Exploratory biomarker analyses on peripheral blood samples may include, but not limited to, immunophenotyping of PBMC and T cell subsets, circulating cytokine and chemokine analysis, TCR repertoire diversity analysis, and gene expression analysis by next generation sequencing (e.g., RNA-seq), and other molecular assessments (e.g., reference sequence for determination of TMB by whole exome sequencing). Specifically, immunophenotyping analysis will focus on, but not limited to, T (CD3, CD4, CD8, Treg), B, NK cells, T cell memory subsets, and expression of Ki-67, and chemokine/cytokine receptor and immune checkpoints or costimulatory regulators.

6.4.2. Pharmacokinetics and Immunogenicity Assessments

PK and Immunogenicity samples for NT-I7 will be collected from all subjects. PK samples will be analyzed for NT-I7 using validated assays.

Serial samples will be assessed following the PK timepoints in Table 3. All time points are relative to the start of study drug administration. Pre-dose samples should be taken within 1-hour PRIOR to administration of study agent(s). If it is known that the dose is going to be delayed, then the pre-dose sample should be taken just prior to delayed dose. However, if the pre-dose sample is collected and dosing is subsequently delayed, an additional pre-dose sample does not need to be collected if pre-dose sample collection and delayed dosing occurs on the same day.

All on-treatment time points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the sampling should be adjusted accordingly.

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

Table 3: Pharmacokinetic (PK) and Immunogenicity Sample Collections*

Treatment Cycle/Visit	Cycle 1				Cycle 2	Cycle 3		Cycle 4	Cycle 5		Cycle 7	Cycle 9	Subsequent Cycles	End of Tx (EOT)	Safety FU
Scheduling Window	Day 1			Day 8 ±2 days	Day 1 ±2 days	Day 1 ±2 days		Day 1 ±2 days	Day 1 ±2 days		Day 1 ±2 days	Day 1 ±2 days	Day 1 ±2 days		90 days after last dose ±7 days
Hours	0 h	2 h (±15mins)	6 h (±30mins)			0 h			0 h						
NT-I7 PK	X[a]	X[b]	X[b]	X	X[a]	X[a]		X[a]	X[a]					X	
NT-I7 ADA[c]	X[a]				X[a]	X[a]			X[a]		X[a]	X[a]	Every 4 Cycles[a]	X[d]	X[e]

[a] PK and immunogenicity samples shall be collected for NT-I7 in all subjects prior to study agent(s) administration on a dosing day, preferably within 1 hour of dosing.
[b] Blood draws are timed after NT-I7 administration is complete.
[c] Immunogenicity samples shall be collected pre-dose on C1D1, C2D1, C3D1, C5D1, C7D1, and C9D1. Thereafter, samples shall be collected pre-dose on every 4 cycles such as C13D1, C17D1, C21D1, and so on, and at time End-of-Treatment (EOT) visit.
[d] End-of-treatment (EOT) testing can be omitted if the last ADA sample collection is within 2 weeks of EOT visit.
[e] Repeat testing at 90-day Safety follow-up visit, if positive at the EOT visit or the last cycle testing (if within 2-weeks of EOT), whichever is applicable.
* Details on blood collection, handling, and shipping are provided in the *NIT-119 Generic Laboratory Manual*.

6.5. Residual Sample Storage for Additional Research

This protocol will include residual sample storage for additional research (AR).

All residual samples will be stored for future use, either a) to be re-purposed for other correlative studies as outlined in this protocol, or b) for as yet undefined research aims that will advance our understanding of disease and options for treatment. It may be used to support health authority request for analysis and advancement of pharmacodiagnostic development to better target drugs to the right subjects. This may also include genetic/genomic exploration aimed at exploring disease pathways, progress, and response to treatment, etc.

Sample Collection and Storage:

Samples kept for future research will be stored at the NIT-approved biorepository. The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by NeoImmuneTech, Inc. to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the subject identifying information. This information is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

7. Study Treatment

Patients will receive NT-I7 and atezolizumab in this study.

7.1. Study Treatment Administration

Reported AEs and potential risks are described in Section 9.1. Appropriate dose modifications are described in Section 7.2.1 and 7.2.2. 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 4: Study Treatment Details

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
NT-I7	None specific for NT-I7, but the below can be given prior to NT-I7 dosing[1]	1200 µg/kg	IM	Day 1 of Q6W	21 days
Atezolizumab	antihistamines or antipyretics/ analgesics[1]	1200 mg	IV	Day 1 of Q3W	21 days

Abbreviations: IM=intramuscular; IV=intravenous.

1 Not permitted for the first dose. Optional for subsequent infusions.

7.1.1. 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.

7.1.1.1. 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. Protect from direct light by storing in the original carton until the time of use. Access to study treatments will be restricted to authorized personnel only.

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

7.1.1.2. NT-I7 Dosing

Subjects will receive NT-I7 IM Q6W.

The NT-I7 dose will be administered 45 (±15) minutes after atezolizumab on days where concurrent administration is planned.

NT-I7 dose administered will be determined using the subject's body weight obtained at the baseline (screening) evaluation. Dosing is by actual body weight. Weight must be re-assessed prior to each NT-I7 dosing; if the subject's weight changes +/- 10% from baseline (screening visit), NT-I7 dose volume will be recalculated based on the new weight measurement.

For obese subjects (BMI ≥ 30), dosing will be determined by adjusted body weight. Proceed with the following steps:

1. **Determine Ideal Weight (1 kg = 2.2 lbs):**
   Males: 50 kg + 2.3 kg x (inch over 5 feet)
   Females: 45.5 kg + 2.3 kg x (inch over 5 feet)
   (Subjects less than 5 feet: subtract 2.3 kg/inch under 5 feet)

2. **Determine Adjusted Body Weight**:
   Ideal Weight + 0.4 x (actual weight – ideal weight) = adjusted body weight

Syringes of NT-I7 will be prepared by the investigational pharmacy according to the dose assignment of the subject. Round doses to the nearest hundredth of an mL. Dose volumes greater than 1 mL may be divided into 2 or more injections (refer to the *NT-I7 Pharmacy Manual* for dose preparation instructions).

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

Injection-related supplies (e.g., syringes, needles) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

Subjects will have their vital signs (heart rate, respiratory rate, blood pressure, and temperature) determined within 60 minutes of NT-I7 administration, if dosing is planned.

7.1.2. Atezolizumab

Atezolizumab 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 45 ± 15 minutes post administration of Atezolizumab on days where concurrent administration is planned*]. Atezolizumab may

be administered up to 2 days before or after the scheduled administration date of each cycle due to administrative reasons.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, the subject's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated for subsequent infusions. Subjects will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for SC, IV, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters and tape

Procedures

In the event of a suspected anaphylactic reaction during atezolizumab infusion, the following procedures should be performed:

- Stop the study drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine or other medications as required by subject status and directed by the physician in charge.
- Continue to observe the subject and document observation.

7.2. Dose Modification

7.2.1. 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 immune-related (ir) AEs 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 not yet fully evaluated in the clinical setting. No irAEs were reported in previous clinical studies with rhIL-7, or with NT-I7 monotherapy, 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). However, 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.

Nevertheless, 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 (32). 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 (e.g., 1 to 2 mg/kg/day PO or IV equivalent), mycophenolate, or TNF-α antagonists (26, 32).

Dose modifications for Adverse Events: If a subject experiences a clinically significant and/or unacceptable toxicity, dosing should be interrupted, or the dose reduced 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 9.2.1). The lowest doses that may be administered are:

- NT-I7 960 μg/kg Q6W
- NT-I7 480 μg/kg Q6W

For a Grade 1 AE, no dose modification is needed.

For a Grade 2 AE related to NT-I7, withhold administration of NT-I7 until the AE is resolved to ≤Grade 1 (see Section 7.3 for criteria to resume treatment).

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 7.3 for criteria to resume treatment), then decrease one dose level to 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 to 480 μg/kg IM Q6W.

Dose re-escalation to 1200 μg/kg IM Q6W is allowed after it is discussed with and approved by the Medical Monitor and the Sponsor.

7.2.2. Dose Modification of Atezolizumab

No dose modifications of atezolizumab is allowed.

Subjects may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for >84 days beyond the scheduled date of infusion, the subject will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the subject is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the protocol PI in consultation with NeoImmuneTech, Inc's designee.

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the risk-benefit balance a given subject may be experiencing prior to further administration of atezolizumab. In subjects who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the subject is deriving benefit and has fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

For detailed information regarding management of AEs associated with atezolizumab, please refer to the most current version of the Atezolizumab IB.

Please see Section 7.2.3 for details regarding management of specific AEs. Assessment of the risk-benefit should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given subject may be experiencing before further administration of atezolizumab. Atezolizumab should be permanently discontinued in subjects with life-threatening irAEs.

Subjects should be assessed clinically (including review of laboratory values) for toxicity before, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

7.2.3. Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, nephritis, meningoencephalitis, myocarditis, myositis, potential ocular toxicities, and severe cutaneous adverse reactions are presented in the Atezolizumab IB. See Section 7.2.3.13 for guidelines for the management of Infusion-Related Reactions (IRR) and Cytokine-Release Syndrome (CRS).

7.2.3.1. Hemophagocytic Lymphohistiocytosis and Macrophage Active Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Subjects with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A subject should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C

- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/L (100,000/μL)
  - ANC < 1.0×10^9/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Subjects with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (33). A febrile subject should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Subjects with suspected HLH or MAS should be treated according to the guidelines in Table 5.

Table 5: Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (34-36). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

7.2.3.2. Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Subjects will be assessed for pulmonary signs and symptoms throughout the study and will have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

Table 6: Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL - bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.3. Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 7.

Subjects with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The subject should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should

be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels, function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test), and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 7: Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider subject referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider subject referral to endocrinologist.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole, as needed. • Consider referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

Table 7 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and subject is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or subject is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If subject has Type 1 diabetes, treat as a Grade 3 event. If subject does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

Table 7 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer subject to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement, if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.4. Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any subject presenting with signs or symptoms suggestive of meningitis or encephalitis, including but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All subjects being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Subjects with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

Table 8: Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer subject to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.5. Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent-atezolizumab. Subjects may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 9.

Table 9: Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer subject to neurologist. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer subject to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.6. Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Subjects eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 10.

Subjects with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For subjects with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 10: Management Guidelines for Hepatic Events

Table 10: Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider subject referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT - liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.7. Gastrointestinal Event

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 11.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-

phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 11: Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Subject referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

Table 11: Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer subject to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. Subjects can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

7.2.3.8. Ocular Event

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 12.

Table 12: Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer subject to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.9. Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible subjects must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Subjects with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the subject to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Subjects with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13: Management Guidelines for Renal Events

Event	Management

Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer subject to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by both the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.10. Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Subjects with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 14: Management Guidelines for Immune-Mediated Myositis

Event	Management

Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer subject to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer subject to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

Table 14: Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer subject to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact Medical Monitor.[c]
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer subject to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.11. Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 15.

Table 15: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise if needed.

Table 15: Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer subject to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. Subjects can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

7.2.3.12. Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 16.

Table 16: Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer subject to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis • Confirm diagnosis by referring subject to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.13. Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 17.

Table 17: Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2, 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of risk-benefit by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator.
Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

7.2.3.14. Immune-Mediated Pericarditis

Immune-mediated pericardial disorders are now considered an identified risk for atezolizumab. Pericardial disorders encompass a range of diseases of the pericardium including pericarditis, pericardial effusion and cardiac tamponade. Underlying causes include infection (particularly viral), cancer-related (metastatic disease or chest radiotherapy), cardiac injury-related (post myocardial infarction or iatrogenic) and autoimmune disorders. Pericardial disorders are also known to be associated with drugs including immune-checkpoint inhibitors.

Pericarditis may be associated with pericardial effusion, which if significant in volume may result in hemodynamic instability and progress to cardiac tamponade. Cardiac tamponade is a life-threatening condition and should be treated as a medical emergency.

The following actions are recommended for management of immune-mediated pericarditis:

- The diagnosis of immune-mediated pericarditis should be considered in all patients presenting with chest pain.
- The diagnosis of immune-mediated pericardial effusion and cardiac tamponade should be considered in all patients presenting with chest pain associated with dyspnea or hemodynamic instability.
- Cardiac tamponade should be treated as a medical emergency and consultation with a cardiologist should be sought for further management.
- Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
- If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
- Atezolizumab should be withheld for patients with suspected immune-mediated pericardial disorders.
- Atezolizumab should be permanently withdrawn for any grade confirmed immune-mediated pericardial disorders.
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a pericardial disorder on prior treatment with other immune-stimulatory anticancer agents.

7.2.3.15. Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, subjects who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (37). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (38, 39), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 18.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (40). If a subject develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 18: Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in subjects with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Table 18: Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in section 7.2.3.1. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in section 7.2.3.1. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize subject until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit subject to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for subjects who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

Table 18: Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit subject to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For subjects who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize subject until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; IV = intravenous, MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the event. The decision to re-challenge subjects with atezolizumab should be based on investigator's assessment of risk-benefit and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after considering the risk-benefit ratio.

[f] Refer to (41).

7.3. Criteria to Resume Dosing

Subjects may resume treatment with atezolizumab and 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 retreatment if discussed with and approved by the Medical Monitor.
- 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 treatment after consultation with the Medical Monitor.

Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the NIT designee must be consulted. 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.

If AEs do not resolve to Grade 1 or baseline by the next planned NT-I7 dose, both atezolizumab and NT-I7 treatments will be delayed. Please see rescheduling rules in Section 7.4.

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

7.4.1. Discontinuation of Study Intervention

In the absence of treatment delays due to AE(s), treatment with NT-I7 and atezolizumab 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
- 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 7.3)
- The patient becomes pregnant. Refer to Section 9.4.
- 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 Atezolizumab 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 Atezolizumab

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 every 60-90 days (± 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.

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.

7.4.2. 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:

- 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.

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.

7.4.3. 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.

7.5. 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.

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 3) disease progression should be confirmed by the site 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 in Appendix 3, 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 (Table 2).

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 3, 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 Appendix 3.

7.6. Post Study Access to Study Treatment

Subjects who continue to receive clinical benefit after 24 months from the date of first dose, may continue to receive the treatment on this study, via a rollover study requiring approval by the responsible Health Authority (HA) and ethics committee, or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study treatment if any of the following occur:

- The marketing application is rejected by the responsible HA.
- The study is terminated due to safety concerns.
- The subject can obtain medication from a government-sponsored or private health program.
- Therapeutic alternatives become available in the local market.

7.7. Blinding/Unblinding

Not applicable.

7.8. Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

7.9. Destruction of Study Drug

For this study, study drugs such as partially used study drug containers, vials, and syringes may be destroyed on site per the site's Pharmacy SOPs and federal, state, and local regulations.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to NIT upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for the return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7. 10. Return of Study Drug

If study drug will not be destroyed by site upon completion or termination of the study, all unused and/or partially used study drug that was supplied by NIT must be returned to study drug vendor. The return of study drug will be arranged by the responsible Study Monitor.

8. Concomitant and Prohibited Medications and Foods

The following sections apply to both dose escalation phase and Phase II of the study.

8.1. Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Any concurrent anti-neoplastic therapy (i.e., antineoplastic systemic chemotherapy or biological therapy, immunotherapy, hormonal therapy, extensive, non-palliative radiation therapy, or standard agents)
- Investigational agents other than NT-I7 and atezolizumab
- 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 150 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 for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
  Note: Use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
  Note: Adrenal replacement steroids > 10 mg daily prednisone equivalent are permitted.
  Note: A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Immunostimulatory and immunosuppressive agents
- No data exist regarding the interaction of NT-I7 with commonly used herbal or non-traditional medications. Caution should use regarding the use of herbal or non-traditional medications as there may be as yet unknown interactions with NT-I7 and/or atezolizumab. Discontinuation of the use of herbal or non-traditional medications prior to study enrollment is encouraged. Subjects should be instructed not to use such medications while receiving atezolizumab and/or NT-I7 treatment.

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.

8.2. 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 atezolizumab and/or NT-I7 treatment should be closely monitored.

8.3. Other Restrictions and Precautions

Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study treatment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

It is the local imaging facility's responsibility to determine, based on subject attributes (e.g., allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (i.e., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

8.4. Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in subjects with bone metastases is allowed if initiated prior to the first dose of study treatment. These agents are prohibited after the start of dosing because preclinical data suggests that they can have immunomodulatory effects, and this can confound the pre-treatment vs. post-treatment biomarker analyses if they are started after first dose.

Prior palliative radiotherapy must have been completed at least 2 weeks prior to the first dose of 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.

All concomitant medication 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 28 days (4 weeks) prior to the first dose of study treatment and up to 90 days after the last dose of study treatment should be recorded. Concomitant medications administered 90 days after the last dose of study treatment should be recorded for SAEs and adverse events of special interest (AESI) as defined in Section 9.3.

8.5. Meals and Dietary Restrictions

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

8.6. Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Refer to Section 7.1.2 for treatment of atezolizumab infusion reactions.

9. Adverse Events: Assessing and Reporting Requirements

9.1. Adverse Events Definition and Collection

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 90 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 9.2.1.

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 characteristics of an observed AE will determine whether the event requires expedited reporting to the Sponsor or designee.

Per GCP, all sites must enter data in a timely manner as agreed for this study. AEs meeting the criteria of SAE (Section 9.2) 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.

9.1.1. Severity

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.

9.1.2. Causality

Attribution of the AE will be graded as follows:

- 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

9.2. 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 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 (saereporting@amarexcro.com and NIT119@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, Amarex, by telephone at + 1 240 454 6844 and/or fax at + 1 240 454 6602. 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.

9.2.1. Time Period and Frequency for Collecting SAE, AESI and Other Reportable Safety Event Information

- SAEs from the time of consent/ allocation through 90 days following cessation of study treatment must be reported by the investigator.

- All AEs from the time of treatment/allocation through 90 days following cessation of study treatment 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 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.

9.2.2. 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 treatment requires both 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 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"* under the system organ class (SOC) of the same name. 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.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators must 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 any 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).

9.3. Adverse Events of Special Interest (AESI) for NT-I7 and Atezolizumab

9.3.1. AESI for 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 the 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. (42)
- Conditions (regardless of grade) suggestive of an autoimmune disorder, including but not limited to hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies (including but not limited to thyroiditis, Type 1 diabetes mellitus, adrenal insufficiency), 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)

9.3.2. AESI for Atezolizumab

The following AEs are of special interest in subjects receiving atezolizumab and must be reported by the investigator expeditiously to the Sponsor and/or Sponsor's safety designee irrespective of regulatory seriousness criteria:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)

- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

9.4. 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 female subject or a female partner of a male subject's from the time of consent to 150 days after the last dose of study treatment must be reported to Sponsor or designee and then followed for outcome. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. 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.

9.5. Use in Nursing Women

It is unknown whether NT-I7 and/or atezolizumab 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.

9.6. 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.

- 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.

9.7. 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. (42)

10. Data Monitoring Committee

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 review data at the Interim Analysis and make the decision whether the study can proceed to Stage 2 or should be terminated due to futility. 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.

11. Ethical Considerations

11.1. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to NIT immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

11.2. Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or NeoImmuneTech, Inc. should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or NeoImmuneTech, Inc. (or designee) should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

11.3. Investigator's Responsibilities

The investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to Roche.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

11.4. Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

NeoImmuneTech, Inc. (or designee) will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects’ signed HIPAA Authorization.

The consent form must also include a statement that NIT and regulatory authorities have direct access to subject records.

12. 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.

12.1. Sample Size and Power Calculation

This Phase II study will enroll a minimum of 26 evaluable subjects and a maximum of approximately 76 evaluable subjects; taking into account a non-evaluable rate of approximately 5% it is planned to enroll up to 83 subjects.

The study will follow Simon's 2-stage optimal design (R. Simon, Controlled Clinical Trials 10:1-10 (1989)) with null ORR test rate 21% and alternative ("promising") rate 35%, powered at approximately 80% for 1-sided alpha = 0.05 primary test with 76 evaluable subjects for the final analysis and interim analysis for futility at 26 evaluable subjects.

Rationale for assuming the null ORR test rate of 21%:

CITYSCAPE study reported an ORR=21% for atezolizumab monotherapy in 1L NSCLC patients with PD-L1 expression of TPS≥1% (1).

12.2. Stratification Factor for Randomization

No stratification is planned.

12.3. Interim Analyses

The futility interim analysis for the Simon optimal design will be conducted at 26 evaluable subjects.

12.4. Statistical Analysis Plan Summary

Study Design Overview	A multicenter, open-label, single-arm Phase II study to evaluate anti-tumor efficacy and safety of NT-I7 (efineptakin alfa) in combination with atezolizumab in subjects with previously untreated, PD-L1-expressing (TPS≥1%), locally advanced or metastatic Non-Small Cell Lung Cancer
Analysis Populations	Safety: All-Subjects-as-Treated (ASaT) Efficacy: All evaluable subjects for primary endpoint ORR per RECIST 1.1 and iRECIST Subjects are required to complete at least Cycle 1 treatment and at least one post-baseline tumor scan to be considered evaluable. The primary efficacy analyses will be based on all treated population and exploratory analyses on the evaluable population.

Primary Endpoint(s)	• Objective Response Rate (ORR), defined as the percentage of subjects with the best overall response (BOR) of a complete response (CR) or partial response (PR) per RECIST 1.1 and iRECIST as determined by the investigator.
Secondary Endpoints	• Duration of response (DoR), 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. *Note: DoR will be assessed statistically via Kaplan-Meier methods and presented descriptively for the responders. Comparative inferential 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 stable disease (SD), per RECIST 1.1 and iRECIST as determined by the investigator. *Note: DCR will be assessed inferentially via Fisher Exact tests supported by Clopper-Pearson confidence interval all analyses will be interpreted descriptively. Comparative assessments are not planned on this endpoint.* • Progression Free Survival (PFS), 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. *Note: PFS will be assessed via Kaplan-Meier methods and presented descriptively for all treated subjects; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively. Comparative inferential assessments are not planned on this endpoint.* • Overall survival (OS), defined as the time from first study treatment (Cycle 1, Day 1) to death from any cause. *Note: OS will be assessed statistically via Kaplan-Meier methods and presented descriptively for all treated subjects; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively. Comparative inferential assessments are not planned on this endpoint.*
Statistical Methods for Efficacy Analysis	Primary: The primary analysis for ORR will include the hypothesis test per Simon design (see Section 12.1 Sample Size and Power Calculation). In addition, the ORR will be estimated with 95% Clopper-Pearson confidence intervals.

	Note: In addition to the primary analyses on the population of treated subjects for the primary endpoints, exploratory analyses will also be presented on the population of all subjects evaluable on study. Secondary: • Duration of response (DoR) for the responders, 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 and iRECIST as determined by the investigator. DoR will be assessed statistically via Kaplan-Meier methods and presented descriptively for the responders. Inferential assessments are not planned on this endpoint. • Disease Control Rate (DCR) is 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 Clopper-Pearson confidence intervals; all analyses will be interpreted descriptively. Inferential assessments are not planned on this endpoint. • Progression Free Survival (PFS), 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; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively. Inferential assessments are not planned on this endpoint. • Overall survival (OS), defined as the time from first study treatment (Cycle 1, Day 1) to death from any cause. OS will be assessed statistically via Kaplan-Meier methods and presented descriptively for all treated subjects; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively.
Treatment Assignment	• All subjects will receive the combination therapy in this single arm design.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.
Multiplicity	No multiplicity adjustment is planned for multiple analyses on this Phase II study.
Sample Size and Power	This Phase II study will enroll a minimum of 26 evaluable subjects and a maximum of approximately 76 evaluable subjects; taking into account a non-evaluable rate of approximately 5% it is planned to enroll up to 83 subjects. The study will follow Simon's 2-stage optimal design ((31)) with null ORR test rate 21% and alternative ("promising") rate 35%, powered at

	approximately 80% for 1-sided alpha = 0.05 primary test with 76 evaluable subjects for the final analysis and interim analysis for futility at 26 evaluable subjects.

13. List of 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
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area Under Concentration
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Amino Transferase
BAL	Bronchoscopic alveolar lavage
BCG	Bacillus Calmette–Guérin
BiPAP	Bi-level positive airway pressure
BUN	Blood Urea Nitrogen
CAR	Chimeric antigen receptor
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
C_{max}	Maximum Concentration
CNS	Central Nervous System
CPAP	Continuous positive airway pressure
CPI	Check Point Inhibitor
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRS	Cytokine-Release Syndrome
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
D1	Day 1
DCR	Disease Control Rate
DL	Dose Level
DSMC	Data Safety Monitoring Committee
DOR	Duration of Response
EAC	Esophageal adenocarcinoma
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

eGFR	Epidermal growth factor receptor
EOT	End of Treatment
ER	Estrogen Receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
FISH	Fluorescence in situ hybridization
FT3/FT4	free Triiodothyronine/ free Thyroxine
FU	Follow Up
GCP	Good Clinical Practice
GEJ	Gastro-esophageal junction
GI	Gastrointestinal
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLH	Hemophagocytic Lymphohistiocytosis
HR	Hazard Ratio
hyFC	hybrid Fc
ICF	Informed Consent Form
ICH	International Council for Harmonization
iCPD	Confirmed Progressive Disease (per iRECIST)
iCR	Complete Response (per iRECIST)
ICU	Intensive Care Unit
IHC	Immunohistochemistry
IM	Intramuscular
IME	Important Medical Events
IND	Investigational New Drug Application
INR	International Normalized Ratio
iPR	Partial Response (per iRECIST)
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-related reaction
iSD	Stable Disease (per iRECIST)
ITT	Intent-To-Treat
iUPD	Unconfirmed Progressive Disease (per iRECIST)
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver function test
LLN/ULN	Lower Limit of Normal/Upper Limit of Normal
mAb	Monoclonal Antibody
MAS	Macrophage Activation Syndrome
MDS	Myelodysplastic Syndrome
MED	Maximum Effective Dose
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability High

MTD	Maximum Tolerated Dose
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NIT	NeoImmuneTech
NKT	Natural Killer-T cells
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
NT-I7	rh-IL-7-hyFc; also known as efineptakin alfa
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
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	Pharmacokinetic
RCC	Renal Cell Carcinoma
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 1.1	Response Evaluation Criteria in Solid Tumors 1.1
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
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
$T_{1/2}$	Terminal half-life
T_{CM}	central-memory T cell
T_{EM}	effector-memory T cell
T_{EMRA}	terminally differentiated effector memory T cells
T_{max}	Time to reach C_{max}
T_{Regs}	regulatory T cells
TEAE	Treatment Emergent Adverse Event

TIL	Tumor-infiltrating lymphocyte
TNF	Tumor Necrosis Factor
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
Tx	Treatment
US PI	United States Prescribing Information
VOP	Verification of Progression
WBC	White Blood Cells

14. References

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15.Appendices

15.1. Appendix 1: ECOG Performance Status

ECOG Performance Status[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a]Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

15.2. Appendix 2: RECIST 1.1 GUIDELINES

RECIST 1.1 guidelines (43) will be provided separately.

15.3. Appendix 3: iRECIST GUIDELINES

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs (44). 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 19. 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.

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

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 whether 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 19, 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 19.

A description of the adaptations and iRECIST process is provided in the latter half of Appendix 3, with additional details in the iRECIST publication. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 19.

Figure 8: Imaging and treatment for clinically stable subjects treated with NT-I7 + atezolizumab after first radiologic evidence of PD assessed by the investigator

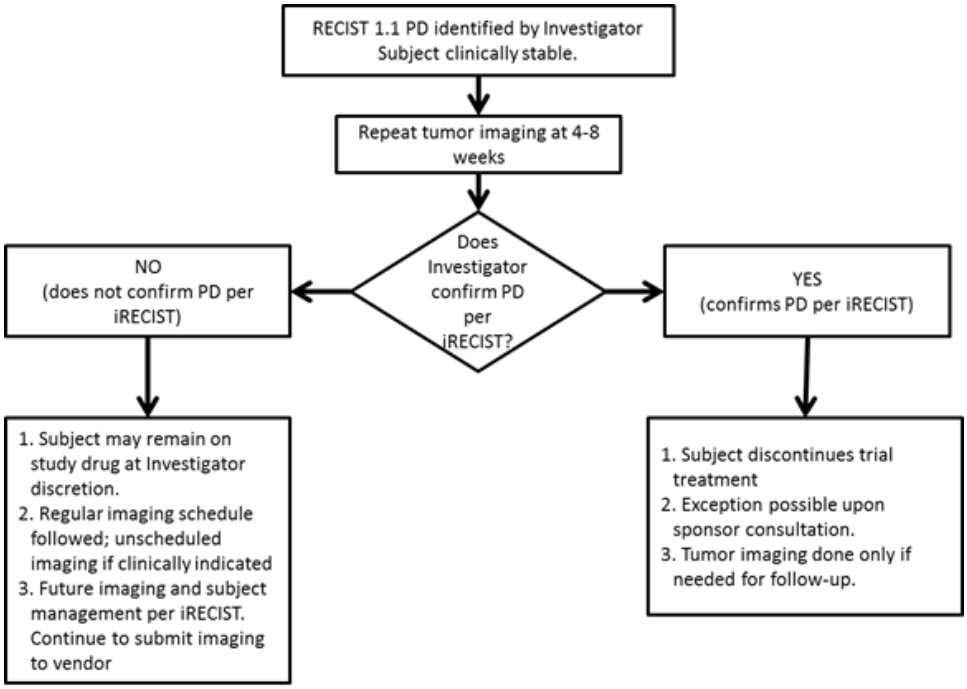

Table 19: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

		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	No additional imaging required.	Not applicable	

		Clinically Stable		Clinically Unstable	
		Imaging	**Treatment**	**Imaging**	**Treatment**
		consultation with Sponsor).			
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 19)**.** This decision by the Investigator should be based on the subject's overall clinical condition.

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 7.5.

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

15.4. Appendix 4: New York Heart Association Functional Classification

This classification has been reproduced from https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

Class	**Patient Symptoms**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective Assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

15.5. Appendix 5: Atezolizumab Adverse Event Management Algorithms

Atezolizumab AE Management Algorithms will be provided separately.