STUDY SUMMARY

Name of Sponsor: NeoImmuneTech, Inc.

Name of Finished Product: NT-I7

Name of Active Ingredient: rhIL-7-hyFc

Title of Study: A Multicenter, Open-label, Phase 2 Study of NT-I7 in Combination with Nivolumab in Subjects with Relapsed/Refractory Gastric or Gastro-Esophageal Junction or Esophageal Adenocarcinoma who Progressed on or Intolerant to 2 or more Prior Lines of Systemic Therapy

Study Centers: Four (4) US sites and two (2) EU (Poland) sites

Publication (Reference): Not applicable

Studied Period: 21-Jan-2021 to 26-May-2023	**Phase of Development:** Phase 2 **Justification of Early termination in Phase 1:** The decision is based on company strategy instead of the safety concern or product efficacy profile, and the NT-I7 risk-benefit profile remains the same.

Objectives:

Primary

- Dose Escalation: To evaluate the safety and tolerability of NT-I7 in combination with nivolumab, including estimation of the maximum tolerated dose and/or the recommended Phase 2 dose (RP2D) in subjects with advanced or metastatic solid tumors
- Phase 2: To assess the antitumor activity of NT-I7 in combination with nivolumab in subjects with relapsed/refractory gastric or gastro-esophageal junction (GEJ) or esophageal adenocarcinoma (EAC) after ≥2 lines of systemic therapy, based on the objective response rate (ORR) per the Independent Review Committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Methodology:

Objectives will be assessed using the following endpoints:

Primary

- Dose Escalation:
  - Incidence and severity of adverse events (AEs), drug-related AEs, and AEs leading to discontinuation of the study drug, graded by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0
  - Incidence and severity of dose-limiting toxicities (DLT)
- Phase 2:
  - ORR, defined as the percentage of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST 1.1, as determined by the IRC

Number of Patients (Planned and Analyzed):

Planned: In the dose-escalation part of the study, enrollment was planned for up to 18 subjects; in the Phase 2 part of the study, enrollment was planned for up to 50 subjects.

Analyzed: A total of 10 subjects were enrolled and included in the analyses.

Criteria for Inclusion:

Subjects had to meet all the following criteria for study entry:

1. Must have been willing and able to sign the informed consent form (ICF)

2. Must have been ≥ 18 years old on the day ICF was signed
3. Subjects enrolling in the dose-escalation phase must have had histologically or cytologically confirmed, locally advanced or metastatic solid tumor and could be either checkpoint inhibitor (CPI)-pretreated or CPI-naïve
4. For the Phase 2, 1) subjects must have had histologically or cytologically confirmed locally advanced or metastatic gastric, GEJ, or EAC and 2) progressed on 2 or more prior lines of standard therapy, including chemotherapy, immunotherapy, or targeted therapy. Note: radiological confirmation on prior therapy was required at least 4 weeks from the initial disease progression. The screening scans could be used as confirmation. Progression following targeted therapy or other approved or investigational therapies was allowed.

   Note: GEJ adenocarcinoma was defined as tumors whose center was within 5 cm proximal and distal of the anatomical cardia, as described in the Siewert classification system.
5. Subjects must have had at least 1 measurable lesion according to RECIST 1.1. A previously irradiated lesion could be considered a target lesion if it was well defined, measurable, and there was objective evidence of an interval increase in size.
6. Subjects enrolling in the dose-escalation phase may have had biopsiable disease (i.e., had at least 1 tumor lesion that was accessible and feasible for biopsy) as determined by the investigator. It was optional for subjects to provide a) pre-treatment tumor tissue sample, either from a previous surgery or biopsy, after the last prior anticancer treatment or a freshly obtained biopsy, prior to the start of treatment in this study, and b) an on-treatment tumor biopsy.
7. In the Phase 2 part of the study, at least 20 subjects were required to provide a tumor tissue sample. These subjects must have had disease that was amenable to biopsy (i.e., at least 1 tumor that was accessible and feasible for biopsy) as determined by the investigator. These 20 subjects must have agreed to provide a pretreatment tumor tissue sample and an on treatment biopsy. Fresh tumor biopsies were preferred and should have been preferentially obtained from tumors that were safely accessible as determined by the investigator, and achieved via nonsignificant risk procedures. Tumors used for biopsy should not have been those used as RECIST 1.1 target lesions. Sites were encouraged to confirm adequacy of tumor biopsy material at the time of the procedure. Archival samples could be accepted as pretreatment samples when freshly obtained biopsies were not possible. A formalin-fixed, paraffin-embedded tissue block (preferred) or a minimum of 15 unstained slides of tumor tissue from a core, punch, or excisional biopsy, or a surgical specimen obtained during screening or after the last treatment and prior to initiation of study treatment (within 3 months of enrollment), must have been sent to the central laboratory. Fine needle aspirates or other cytology samples were not acceptable as fresh or archival samples.
8. Eastern Cooperative Oncology Group performance status of 0-1
9. Life expectancy greater than or equal to 12 weeks, per the investigator's assessment
10. Adequate organ and marrow function as defined below. Criteria a, b, and c could not have been met with ongoing or recent blood transfusions (within 14 days of starting the first dose) or require growth factor support (within 28 days [4 weeks]) of starting the first dose:
    a. Absolute neutrophil count ≥1500/μL
    b. Platelets ≥100,000/μL
    c. Hemoglobin ≥9.0 g/dL
    d. Total bilirubin ≤1.5 × the upper limit of normal (ULN) OR direct bilirubin ≤ULN for subjects with total bilirubin concentration >1.5 × ULN (except if bilirubin elevation was due to Gilbert syndrome)
    e. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤3 × ULN (AST and/or ALT ≤5 × ULN for subjects with liver metastasis)

f. Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN for subjects with documented liver involvement or bone metastases)

g. Creatinine clearance ≥40 mL/min/1.73 m^2 by the Cockcroft-Gault equation. At the discretion of the investigator, a 24-hour urine creatinine clearance could be obtained and used as the gold standard if the creatinine clearance by the Cockcroft-Gault equation was <40 mL/min/1.73 m^2

h. International Normalized Ratio and partial thromboplastin time ≤1.5 × ULN (this applied only to subjects who did not receive therapeutic anticoagulation; subjects receiving therapeutic anticoagulation such as low-molecular weight heparin or warfarin should have been on a stable dose)

11. Female subjects had to be either postmenopausal for at least 1 year, or surgically sterile for at least 6 weeks; if a female subject was of childbearing potential, she had to agree 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 for 5 months after the last dose of study treatment. Female subjects of childbearing potential (including women who have had a tubal ligation) must have had a negative serum or urine pregnancy test within 24 hours prior to Cycle 1 Day 1. If the urine test was positive, or could not be confirmed as negative, a serum pregnancy test was required.

12. Nonsterile male subjects who were sexually active with female partners of childbearing potential must have agreed to remain abstinent (refrained from heterosexual intercourse) or to follow instructions for one highly effective method of contraception for the duration of study treatment and for 3 months after the last dose of study treatment.

Subjects meeting <u>any</u> of the following exclusion criteria were not eligible for inclusion in the study:

1. Pregnant, breastfeeding, or expecting to conceive or father children within the study duration from screening through 5 months (for female subjects) or 3 months (for male subjects) after the last dose of the study treatment.

2. Receiving chemotherapy or any anticancer therapy with a half-life <1 week within 4 weeks or 5 half-lives, whichever was shorter, prior to the first dose of study treatment.

3. Had received prior radiotherapy within 2 weeks of the start of study treatment; subjects must have recovered from all radiation-related toxicities, did not require corticosteroids, and did not have radiation pneumonitis. A 1-week washout was permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.

4. Had received treatment with complementary medications (e.g., herbal supplements or traditional Chinese medications) to treat the disease under study within 2 weeks prior to the first dose of study treatment.

5. Subjects were eligible if CNS metastases were asymptomatic and did not require immediate treatment or had been treated and subjects had neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, subjects must have been either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for at least 2 weeks prior to start of study treatment. Imaging performed within 28 days (4 weeks) prior to the first dose of study treatment had to document radiographic stability of CNS lesions and performed after completion of any CNS-directed therapy.

6. Subjects who had not recovered from AEs (other than alopecia, vitiligo, neuropathy, or endocrinopathy managed with replacement therapy) due to agents administered more than 4 weeks earlier (i.e., residual toxicities Grade >1)

7. Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years before treatment assignment (i.e., subjects with a history of prior malignancy were eligible if treatment was completed at least 2 years before the treatment assignment, and the subject had no evidence of disease), except for cured basal or squamous

cell skin cancer, transitional cell carcinoma of urothelial cancer, carcinoma in situ of the breast or cervix.

8. History of severe hypersensitivity reactions to monoclonal antibodies (mAbs) or intravenous immunoglobulin preparations, any history of anaphylaxis, 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. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence of clinically stable disease for ≥2 weeks prior to screening.
10. Active known or suspected autoimmune disease, 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-Barré syndrome, multiple sclerosis, vasculitis, or glomerular nephritis.

    Note: Subjects with type 1 diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enroll
11. An active and clinically relevant bacterial, fungal, viral, or tuberculosis infection, including known hepatitis A, B, or C, or human immunodeficiency virus (HIV; testing not required)
12. Clinically significant cardiac disease, including, but not limited to, any of the following: Congestive heart failure requiring treatment (New York Heart Association Grade ≥2); clinically significant and uncontrolled atrial fibrillation; history of acute coronary syndromes including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting <6 months prior to screening; symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening except controlled atrial fibrillation and paroxysmal supraventricular tachycardia
13. Subjects who had received treatment with systemic immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor agents) within 1 week prior to the first dose of study treatment.

    Note: Inhaled, or topical steroids, and steroids doses >10mg/day prednisone or equivalent for adrenal replacement are allowed.
14. History of allergy or intolerance (unacceptable AEs) to the study drug components or polysorbate 80-containing injection

    Note: Polysorbate 80 is a buffer used to make NT-I7.
15. History of noninfectious pneumonitis that required steroids or current pneumonitis
16. 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 was not in the best interest of the subject to participate, in the opinion of the investigator
17. Known psychiatric or substance use disorder that would interfere with the subject's ability to cooperate with the requirements of the study
18. Received a live/attenuated vaccine within 4 weeks 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 (chickenpox), yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and were allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and were not allowed

19. Previous allogeneic tissue/solid organ or bone marrow transplant
20. Subjects who were deprived of liberty by a judicial or administrative decision, subjects were under psychiatric care, and subjects who were under a legal protection measure (guardianship, curatorship, and safeguard of justice)
21. Recently received mAbs and/or mAb-derived therapies within 4 weeks prior to the first dose of study treatment
22. Subjects with a history of inability to tolerate prior CPIs and who were discontinued from that therapy

Test Product, Dose, and Mode of Administration, Batch Number:

	NT-I7	Nivolumab
Study doses	480 to 1200 µg/kg	480 mg
Dosing Regimen	Every 8 weeks	Every 4 weeks
Route of administration	Intramuscular injection	Intravenous infusion

Planned Duration of Treatment: Up to 27 months

Criteria for Evaluation:

Safety Analysis Set:

All subjects who received at least 1 dose of the study medication; this set was used for the dose-escalation phase for all efficacy endpoints, safety, demographic, baseline characteristics, and exploratory endpoints.

Per-Protocol Analysis Set:

All subjects who received at least 1 dose of study medication, had no major protocol violations, and had both baseline and postbaseline tumor assessments; this population was used for all PK analyses in the dose-escalation phase. Subjects for whom death occurred prior to the first postbaseline tumor assessment were to be replaced.

DLT-Evaluable Population:

All subjects in the dose-escalation part of the study who were in the safety population and completed the full 4-week DLT window or who did not complete the full 4-week DLT window due to a DLT.

Statistical Methods:

The dose escalation phase was planned to follow the standard 3+3 study design. Three Dose Groups of NT-I7 were planned [Group 1 (480 µg/kg IM Q8W), Group 2 (840 µg/kg IM Q8W), and Group 3 (1200 µg/kg IM Q8W)], and up to 18 subjects were to be enrolled.

The Phase 2 study was planned to enroll a minimum of 15 and a maximum of 44 evaluable subjects. Taking into account a nonevaluable rate of approximately 10%, it was planned to enroll up to 50 subjects.

The study was planned to follow a Simon's 2-stage optimal design with a null ORR test rate of 10% and alternative ("promising") rate of 22%, powered at approximately 80% for a 1-sided alpha = 0.10 primary test with 44 evaluable subjects for the final analysis and interim analysis for futility at 15 evaluable subjects. With this design, the futility crossing probability under the null hypothesis would be 65.3%.

Study Results

Subject Demographics:

The median age overall was 61.5 years and was similar in each dose group. Most subjects were younger than 65 years. More men were enrolled than women (60% vs 40%). Most subjects were white and not Hispanic or Latino. The overall median body mass index was 25 kg/m^2 and was similar in each group.

Subject Disposition:

Of the 12 screened subjects, 10 were enrolled. The DLT-evaluable set included 100%, 75.0%, and 100% of subjects in Dose Groups 1, 2, and 3, respectively. One subject (Dose Group 3) was in the per-protocol set. All subjects discontinued the study treatment early, and the most common reason was progressive disease. All subjects were discontinued from the study, and the most common reason was death. The median duration of participation in the study was 5.80 months overall.

Summary – Results and Conclusions

Efficacy Results:

Using RECIST 1.1 and iRECIST, 3 subjects had a best overall response of SD and thus met the criteria for unconfirmed DCR; 1 of these subjects was in Dose Group 2 and 2 were in Dose Group 3. No subjects had a CR or PR by RECIST 1.1 or iRECIST. Six subjects had progressive disease (3 subjects in Dose Group 1, 2 subjects in Dose Group 2, and 1 subject in Dose Group 3), and 1 subject's response in Dose Group 2 was not evaluable due to death before a postbaseline tumor assessment could be performed. The percentage of subjects with PFS by RECIST 1.1 at 6 weeks was 80% overall (Dose Group 1: 100%, Dose Group 2: 75%, Dose Group 3: 66.7%), but declined thereafter (at 12 weeks, Dose Group 1: 0% in Dose Group 1, Dose Group 2: 25%, Dose Group 3: 66.7%), and at 30 weeks was 20% (Dose Group 1: 0%, Dose Group 2: 25%, Dose Group 3: 33.3%). Using iRECIST, a similar trend was seen, with an overall PFS of 90% at 6 weeks, declining to 38% at 18 weeks and thereafter. The OS rates appeared to exhibit dose dependence starting at 12 weeks and continuing through 24 weeks, with 66.7%, 75%, and 100% in Dose Groups 1, 2, and 3, respectively. However, the small subject population limits interpretation of the efficacy results.

Safety Results:

All subjects had at least 1 AE; 5 subjects had an AE that was Grade 3 or higher; and 8 subjects had an AE that was related to the study drugs but none of NT-I7 or nivolumab-related AEs were Grade 3 or higher. The most common drug-related AE was pyrexia (3 subjects). Injection site reaction, injection site swelling, and myalgia were reported for 2 subjects each. No other preferred term was reported for more than 1 subject. Five subjects had at least 1 serious adverse event (SAE), but none of the events were related to the study drugs. Three of these subjects had a fatal SAE; however, all 3 were unrelated to the study drugs and related to progression of the underlying disease. A total of 6 subjects had at least 1 AE of special interest and 4 had immune-related AEs. An analysis of AEs did not appear to show a dose -dependent relationship. No meaningful abnormalities or trends were apparent in any laboratory parameter, vital signs, electrocardiograms, or physical examinations. Based on these limited data, it can be concluded that the study drugs were well tolerated in the study population.

Immunogenicity Results:

All evaluable subjects developed anti-NT-I7 antibodies that had neutralizing activity. The titers tend to increase with exposure, but the data were insufficient for an analysis of correlation with efficacy or safety endpoints.

Conclusion:

Due to early termination, this study included only the small set of subjects from the dose escalation phase. There were large intersubjective variations in responses, even within each dose group. The subjects in this study had advanced, metastatic disease at baseline; most developed disease progression during the study, and 4 subjects died of complications of their underlying disease. Although interpretation of the efficacy and safety data are limited, overall, the study did not identify significant safety concerns and the study drugs were well tolerated. Further studies are needed to evaluate the therapeutic effect and safety profile of NT-I7 in combination with nivolumab in subjects with advanced gastric cancer, GEJ cancer, or EAC.

Date of the report: **Final; 04 Apr 2024**