TABELECLEUCEL

STUDY NUMBER: ATA129-NPC-202

An Open-Label Phase 1B/2 Study to Evaluate the Safety and Efficacy of Tabelecleucel in Combination with Pembrolizumab in Subjects with Platinum-pretreated, Recurrent/Metastatic Epstein-Barr Virus-Associated Nasopharyngeal Carcinoma

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Proprietary Notice

INVESTIGATOR AGREEMENT

Study Title: An Open-Label Phase 1B/2 Study to Evaluate the Safety and Efficacy of Tabelecleucel in Combination with Pembrolizumab in Subjects with Platinum-pretreated, Recurrent/Metastatic Epstein-Barr Virus-Associated Nasopharyngeal Carcinoma

Study Number: ATA129-NPC-202

I have read and reviewed the protocol described above. I agree to comply with all applicable regulations including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) (ICH E6) and to conduct the study according to the protocol.

I agree to provide copies of the protocol and the Investigator's Brochures for tabelecleucel (ATA129) and pembrolizumab, which were provided by the sponsor, to all members of the study team. I will insure that they are fully trained regarding the investigational product and the conduct of the study.

I agree to make available to sponsor personnel, their representatives and regulatory authorities, my subjects' study records in order to verify the data that I have entered into the electronic case report forms. I am aware of my responsibilities as a study investigator as provided by the sponsor.

Signature Date

Printed Name

Title

Institution

SYNOPSIS

Study Title

An Open-Label Phase 1B/2 Study to Evaluate the Safety and Efficacy of Tabelecleucel in Combination with Pembrolizumab in Subjects with Platinum-pretreated, Recurrent/Metastatic Epstein-Barr Virus-Associated Nasopharyngeal Carcinoma

Study Number: ATA129-NPC-202

Study phase: 1B/2

Study Objectives

The primary objectives of the study are:

- Phase 1B: To characterize the incidence of dose-limiting toxicities (DLTs) of tabelecleucel (ATA129; allogeneic Epstein-Barr virus cytotoxic T lymphocytes [EBV-CTLs]) in combination with pembrolizumab (checkpoint inhibitor) in subjects with platinum-pretreated, recurrent/metastatic EBV-associated nasopharyngeal carcinoma (NPC)
- To identify the maximum tolerated dose (MTD), or in the absence of an MTD, the recommended phase 2 dose (RP2D) of tabelecleucel when administered in combination with pembrolizumab
- Phase 2: To evaluate the objective response rate (ORR, defined as complete response [CR] or partial response [PR] confirmed ≥ 28 days from the initial response assessment showing a response) obtained following administration of the combination of tabelecleucel and pembrolizumab, where the response evaluation criteria in solid tumors (RECIST) 1.1 response is determined using an independent radiographic review (IRR)
- For both phase 1B and phase 2: To characterize the safety profile of tabelecleucel in combination with pembrolizumab in the NPC subject population

The secondary objectives are:

- To evaluate additional clinically relevant outcomes in subjects with NPC treated with tabelecleucel in combination with pembrolizumab as measured by CR rate, duration of response (duration of response [DOR]; ie, CR + PR), progression-free survival (PFS), and overall survival (OS)
- To evaluate the immune response rate (iRR; ie, immune CR [iCR] + immune PR [iPR] rate) and duration of immune response (DOiR)

The exploratory objectives are as follows:

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Study Design

This is a multicenter, open-label, single-arm study in subjects with platinum-pretreated, recurrent/metastatic EBV$^+$ NPC (also referred to as NPC in this protocol). The study will be conducted in 2 parts: Cohort 1 will be enrolled as the phase 1B portion to determine the phase 2 dose; Cohort 2 will be enrolled as the phase 2 portion to examine the clinical benefits of combined T cell (tabelecleucel) and checkpoint inhibitor (pembrolizumab) immunotherapies for the treatment of subjects with NPC. The study will enroll 48 to 60 subjects in total. Cohort 1 will enroll 12 to 24 subjects. For each dose level explored in Cohort 1, at least 6 subjects must have had disease that is refractory to an anti-PD-1 or PD-L1 monoclonal antibody. All other subjects enrolled into Cohort 1 will be checkpoint inhibitor naïve subjects (have never received pembrolizumab or other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 [CD134], or anti-cytotoxic T-lymphocyte-associated protein-4 [CTLA-4] products). Dose de-escalation is permitted in Cohort 1 only. Cohort 2 will enroll 36 subjects who are checkpoint inhibitor naïve.

Tabelecleucel will be selected for each subject from the bank of available tabelecleucel cell products based on matching ≥ 2 human leukocyte antigen (HLA) alleles, at least one of which is a restricting HLA allele, ie, shared between the tabelecleucel source material (donor) and the subject.

In Cohort 1, tabelecleucel will be administered initially to 12 subjects at a dose of 2 x 10^6 cells/kg intravenously (IV) on Day 1, Day 8, and Day 15 of a 21-day cycle. Pembrolizumab will be administered to adult subjects (≥ 18 years of age) at a dose of 200 mg IV every 3 weeks (Q3W; ie, on Day 1 of each 21-day cycle) and to pediatric (adolescent) subjects (12 to < 18 years of age) at a dose of 2 mg/kg IV Q3W. If ≥ 2 of the initial 6, or ≥ 4 of the initial 12 Cohort 1 subjects experience a DLT in the first 21 days, the dose of tabelecleucel will be reduced to 1 x 10^6 cells/kg/dose, and an additional 12 subjects will be treated with the combination of tabelecleucel at 1 x 10^6 cells/kg/dose and pembrolizumab at the recommended dose level. Otherwise, all 12 subjects in Cohort 1 will receive tabelecleucel at 2 x 10^6 cells/kg/dose and pembrolizumab at the recommended dose level.

A Safety Data Review Committee (SDRC) composed of representatives from the sponsor and the principal investigators or designated sub-investigators from all sites enrolling subjects in Cohort 1 will review reported DLTs and cumulative safety data to determine further enrollment. The data review will occur as soon as possible after Cycle 1 Day 21 of the last subject in Cohort 1. After the SDRC review, 36 subjects will be enrolled in Cohort 2 and treated with the combination at the recommended dose level.

The planned dose cohort populations for the study are:

Cohort	Number of Subjects	Prior Therapy
1	12 to 24	Checkpoint inhibitor naïve [a] or PD-1/PD-L1 failures (ie, refractory to or relapsed after PD-1/PD-L1 treatment) At least 6 of the 12 subjects must have disease that is refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody for each dose level explored
2	36	Checkpoint inhibitor naïve[a] subjects

[a] Checkpoint inhibitor naïve have never received pembrolizumab or other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies

The planned initial dose level (1) and dose de-escalation levels (2) for the study are:

	Tabelecleucel Dose (cells/kg)	Pembrolizumab Adult Dose (mg)	Pembrolizumab Pediatric Dose (mg/kg)
Dose level 1	2×10^6 on Day 1, Day 8, and Day 15	200 on Day 1	2 on Day 1
Dose level 2	1×10^6 on Day 1, Day 8, and Day 15	200 on Day 1	2 on Day 1

During the Treatment Phase, subjects will receive two 21-day treatment cycles of combination immunotherapy and then undergo a response assessment at the Observation Visit. Based on the subject's response to these initial 2 cycles s/he may receive one additional consolidation cycle with the same tabelecleucel product or additional treatment cycles with tabelecleucel with the same or a different HLA restriction, if an appropriately matched product is available. Detailed designs and schema are described in the protocol. At any time during the Treatment Phase if a subject has a confirmed progressive disease (cPD), it is at the investigator's discretion to continue treatment with tabelecleucel with a different HLA restriction (Switch Therapy, if available) without pembrolizumab. A maximum of 4 treatment/consolidation cycles and 1 Switch Therapy will be permitted.

During the Maintenance Phase, subjects will receive tabelecleucel on Day 1 and pembrolizumab on Day 1, Day 21, Day 42, and Day 63 of 84-day maintenance cycles, which will continue until disease progression, unacceptable toxicity, or a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given. After completing an End-of-Treatment (EOT) Visit 30 days after the last dose of investigational product, subjects will enter quarterly follow-up until 12 months after the last dose of investigational product or until disease progression. During this last phase, survival and disease status will be collected through clinic visits or telephone contact. The end-of-study is defined as the date of the last quarterly follow-up.

Definitions

Subject replacement: Subjects who discontinue due to a DLT after receiving both pembrolizumab and tabelecleucel during the 21-day DLT assessment window will not be replaced; however, subjects who discontinue due to a DLT associated with the first infusion of pembrolizumab (ie, prior to any tabelecleucel infusion) will be replaced. Subjects who discontinue from Cohort 1 for any reason other than a DLT prior to completing the 21-day DLT assessment window will be replaced until the required number of evaluable subjects complete the 21-day DLT assessment window. Subjects will not be replaced in Cohort 2.

DLT definition: All toxicities will be graded based on the investigator's assessment using Common Terminology Criteria for Adverse Events (CTCAE) version 5, except for certain events described in the protocol which have a separate grading system. Specific toxicities (defined in the protocol) will be considered DLTs, if they are judged by the investigator to be possibly related or related to either investigational product tabelecleucel and/or pembrolizumab administration, excluding toxicities clearly not related to the investigational product, such as disease progression, environmental factors, unrelated trauma, etc.

The DLT window of observation will be during Cycle 1 of the Treatment Phase (ie, during the first 21-day cycle; adverse events [AEs] meeting the definition of a DLT but occurring after this period will not be considered DLTs).

Any subject experiencing a DLT will be withdrawn from treatment (both investigational products).

MTD definition: The MTD is defined as the highest dose level at which the subject incidence of a DLTs during the first 21-day cycle of investigational product dosing is < 33%.

RP2D definition: The RP2D is no higher than the MTD and is based on optimal benefit-risk, as determined by the SDRC.

Study Population: Up to a total of 48 to 60 subjects will be enrolled in the study. Of the 48 to 60 subjects, 12 to 24 subjects will enroll in phase 1B portion (Cohort 1) of the study, and 36 subjects will be enrolled in phase 2 portion (Cohort 2) of the study.

Subject Enrollment Criteria

Subjects must undergo a tabelecleucel inventory check to ensure availability of an appropriately matched and restricted tabelecleucel cell product prior to undergoing screening procedures. The inventory check includes collection of the subject's high-resolution HLA typing (DNA-based versus serologic assessment) and weight.

Inclusion criteria

A subject will be considered eligible to participate in this study if all of the following inclusion criteria are satisfied:

1. Male or female ≥ 12 years of age

2. Incurable, locally recurrent or metastatic NPC (World Health Organization type II/III) in whom the EBV nucleic acid or antigens have been demonstrated in tissue biopsy samples
3. Subjects must have had prior receipt of platinum-containing regimen, ***either***:
    a. For the treatment of recurrent or metastatic disease, ***or***
    b. Experienced progression of disease within 6 months following completion of a platinum-based combination therapy as part of (neo)adjuvant chemotherapy. Note: Patients who had only concurrent chemoradiation therapy without (neo)adjuvant therapy and then recurred/metastasized must have progressed on at least 1 platinum-containing regimen for their recurrent/metastatic disease before study entry.
4. Phase 1B (Cohort 1):
    a. Checkpoint inhibitor naïve (have never received pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies)

        OR

    b. Refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody approved by the local regulatory agency either as monotherapy or in combination with other checkpoint inhibitors or therapies according to their approved label. To be considered refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody, all of the following criteria must be met:
        i. Received at least 2 doses of anti-PD-1 or anti-PD-L1 monoclonal antibody at a local regulatory agency-approved dose and schedule.
        ii. Have progressive disease after anti-PD-1 or anti-PD-L1 monoclonal antibody as defined according to RECIST 1.1. The initial evidence of progressive disease is to be confirmed by a second assessment, no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression. (The eligibility determination will be made by the investigator and then the sponsor will collect for retrospective analysis at a central vendor. Once progressive disease is confirmed, the initial date of progressive disease documentation will be considered the date of disease progression).
        iii. Documented disease progression within 24 weeks of the last dose of anti-PD-1 or anti-PD-L1 monoclonal antibody. A subject who was re-treated with anti-PD-1 or anti-PD-L1 monoclonal antibody and a subject who was on maintenance with an anti-PD-1 or anti-PD-L1 monoclonal antibody will be allowed to enter the study as long as there is documented progressive disease within 24 weeks of the last treatment date (with the anti-PD-1 or anti-PD-L1 monoclonal antibody).
5. Phase 1B (Cohort 1): If PD-1/PD-L1 failure (ie, refractory to or relapsed after PD-1/PD-L1 treatment), must have a lesion that can be biopsied after administration of tabelecleucel with acceptable clinical risk (as judged by the investigator), and must agree to undergo biopsy before Cycle 1 Day 1
6. Phase 2 (Cohort 2): Checkpoint inhibitor naïve (have never received pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies)

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8. Life expectancy ≥ 4 months at time of screening
9. Measurable disease using RECIST 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been documented in such lesions
10. Eastern Cooperative Oncology Group (ECOG) performance status of < 2 for subjects aged > 16 years; Lansky score ≥ 70 for subjects aged 12 to 16 years

11. Adequate organ function per the following:

System	Laboratory Value
Hematological	
ANC	≥ 1,500/μL
Platelets	≥ 100,000/μL
Hemoglobin[a]	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated creatinine clearance[b] (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x ULN **OR** ≥ 30 mL/min for subject with creatinine levels > 1.5 x ULN
Hepatic	
TBILI	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for subjects with TBILI > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN ≤ 5 x ULN for subjects with liver metastases
Coagulation	
INR or PT aPTT	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance should be calculated per institutional standard.

12. Willing and able to provide written informed consent (pediatric subjects 12 to < 18 years of age must provide assent along with consent from the subject's legally authorized representative)

Exclusion criteria

A subject will not be eligible to participate in the study if any of the following criteria are met:

1. Disease that is suitable for local therapy administered with curative intent
2. Requires vasopressor or ventilator support
3. Received antithymocyte globulin or similar anti-T-cell antibody therapy ≤ 4 weeks prior to Cycle 1 Day 1
4. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to Cycle 1 Day 1 of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor's medical monitor.
5. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
6. History or evidence of interstitial lung disease
7. History of severe hypersensitivity (Grade ≥ 3) to pembrolizumab and/or any of its excipients

8. Active infection requiring systemic therapy
9. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
10. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor or recombinant erythropoietin) within 4 weeks prior to study Day 1
11. Unresolved immunotherapy-related adverse events (AEs) or treatment for these events within 4 weeks prior to enrollment
12. History of severe immunotherapy-related adverse effects (CTCAE grade 4; CTCAE grade 3 requiring treatment > 4 weeks)
13. Received any non-oncology vaccine therapy used for prevention of infectious diseases for up to 30 days prior to enrollment. Examples include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are acceptable
14. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer
15. Pregnancy or breastfeeding: females of childbearing potential must have a negative serum pregnancy test. The serum pregnancy must be confirmed negative within 72 hours of Cycle 1 Day 1 (first dose of investigational product) for the subject to be eligible.
16. Female of childbearing potential or male with a female partner of childbearing potential unwilling to use a highly effective method of contraception (abstinence is acceptable) for the course of the study through 120 days after the last study dose
17. Inability to comply with study procedures
18. Received chemotherapy or targeted small molecule therapy within 2 weeks of Cycle 1 Day 1. Subjects must have recovered (ie, grade ≤ 1 or at baseline) from AEs due to a previously administered agent. Subjects with grade ≤ 2 neuropathy or grade ≤ 2 alopecia are an exception to this criterion.
19. Received prior radiotherapy within 2 weeks of Cycle 1 Day 1. 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-central nervous system (CNS) disease.
20. Antibody/biologic therapy within 4 weeks of Cycle 1 Day 1 or not recovered (ie, grade ≤ 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier
21. Carcinomatous meningitis; and/or active CNS metastases, unless metastases are treated and stable and the subject does not require systemic steroids. NOTE: Subjects with previously treated brain metastases may participate provided the metastases are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to first dose of investigational product 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 7 days prior to first dose of investigational product. This exception only relates to CNS metastases and does not include carcinomatous meningitis which is excluded regardless of clinical stability
22. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
23. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study
24. Known history of human immunodeficiency virus (HIV), known active hepatitis B virus (HBV; eg, hepatitis B surface antigen [HBsAg] reactive), or hepatitis C virus (HCV; eg, HCV ribonucleic acid [RNA] is detected)
25. Prior treatment with any investigational product within 4 weeks of Cycle 1 Day 1

26. Prior treatment with EBV T cells

Test Product, Dose, and Mode of Administration

Pembrolizumab: administered IV at a dose level of 200 mg for adults (≥ 18 years of age) or 2 mg/kg Q3W for children (12 to < 18 years of age). Pembrolizumab will be administered prior to the administration of tabelecleucel. Pembrolizumab will be administered on Day 1 of each 21-day treatment/consolidation cycle and on Day 1, Day 21 (± 2), Day 42 (± 2), and Day 63 (± 2) of each 84-day maintenance cycle.

Tabelecleucel: administered IV at doses of $1\text{-}2\times10^6$ cells/kg. Tabelecleucel will be administered 1 hour (± 10 minutes) after the completion of pembrolizumab. Tabelecleucel will be administered on Day 1, Day 8 (± 2), and Day 15 (± 2) of each 21-day treatment/consolidation cycle and on Day 1 of each 84-day maintenance cycle.

Dosing of both tabelecleucel and pembrolizumab, including dose modification and adjustment, will follow protocol guidance.

Duration of Treatment and Subject Participation

The duration of treatment is dependent on a subject's response to treatment and is estimated to be approximately 2 years for subjects with a response to treatment (CR, PR, or SD), which is a maximum of 4 treatment/ consolidation cycles (21-day cycles with 3 infusions of tabelecleucel and 1 of pembrolizumab) and maintenance cycles (84-day cycles with 4 infusions of pembrolizumab and 1 of tabelecleucel) until up to a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given.

After treatment/consolidation and maintenance cycles, subjects will have an End-of-Treatment visit (30 days after the last dose of investigational product) and then enter Quarterly Follow-up for 12 months after the last dose of investigational product. Before receiving any treatment, subjects must undergo a tabelecleucel inventory check and screening, with screening up to 28 days prior to the first dose of investigational product.

Endpoints

The primary endpoints are:

- The incidence of DLTs in Cohort 1
- The MTD, or in the absence of an MTD the RP2D, of tabelecleucel when administered in combination with pembrolizumab
- The ORR of tabelecleucel in combination with pembrolizumab
- The characterization of the safety profile of tabelecleucel in combination with pembrolizumab in subjects with NPC

Secondary endpoints are:

- CR rate, DOR, PFS, and OS
- iRR (ie, iCR + iPR rate) and DOiR

Exploratory endpoints are:

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Statistical Considerations

Analysis Population

The efficacy and safety populations will include all subjects enrolled in the study and who receive any investigational product. The efficacy population will be for the primary efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics.

In order for a subject to be considered evaluable for the analysis of DLT, the subject should have either had a DLT during the 21-day DLT assessment window or had completed the 21-day DLT assessment. Otherwise, a replacement subject will be added to Cohort 1.

Efficacy Analyses

For estimation purposes, the primary endpoint (ORR) will be analyzed using the exact one-sample binomial test at the 1-sided alpha = 0.025 significance level. A one-sided 2.5% exact test will be used. The null hypothesis is ORR ≤ 20% and the targeted ORR is ≥ 45%. The point estimate of ORR and the corresponding 95% confidence intervals (CI) will be provided. Any checkpoint inhibitor-naïve Cohort 1 subjects treated at the RP2D will be included in the primary efficacy analysis.

The distributions of DOR, PFS, OS, and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Efficacy endpoints that are defined as proportions, including CR rate and iRR, will be summarized using two-sided exact binomial 95% CIs.

The primary analysis of the tumor response-based endpoints will be based on tumor assessments following administration of up to 2 tabelecleucel cell products.

Safety Analyses

Safety assessments will include all related and unrelated AEs. All AEs will be mapped using the Medical Dictionary for Regulatory Activities (MedDRA) and graded by the investigator according to CTCAE version 5, except for certain events described in the protocol which have a separate grading system. AEs will be summarized by the number and percentage of subjects for whom AEs were reported, serious versus non-serious, and investigator-reported relationship (unrelated, possibly related, related). Descriptive statistics will be used to summarize AE types and frequencies.

Sample Size Determination

The estimated ORR for treatment with the combination of tabelecleucel and pembrolizumab is ≥ 45%. The comparator ORR deemed uninteresting is 20%. Based on the exact binomial test at the 1-sided alpha = 0.025 significance level, a sample size of 36 subjects will provide 90% power to detect a true ORR of at least 45%.

Interim Analysis

No interim analysis is planned.

TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

Table of Contents

Synopsis....3
TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES....11
Table of Contents....11
List of Tables....14
List of Figures....15
List of Abbreviations and Definitions of Terms....16
1 INTRODUCTION....19
1.1 Pharmaceutical and Therapeutic Background – Pembrolizumab....19
1.1.1 Preclinical and Clinical Studies....19
1.1.2 Pembrolizumab Background and Clinical Studies....20
1.1.3 Justification for Pembrolizumab Dose....20
1.1.3.1 Rationale for Pembrolizumab Adult Dose Selection....20
1.1.3.2 Rationale for Pembrolizumab Pediatric Dose Selection....21
1.2 Pharmaceutical and Therapeutic Background – Tabelecleucel....21
1.2.1 Tabelecleucel and Epstein-Barr virus-specific cytotoxic T lymphocytes....21
1.2.2 Clinical Experience with Tabelecleucel for EBV^{+} PTLD....22
1.2.3 Justification for Dose....22
1.2.3.1 Dose Selection....22
1.2.3.2 Rationale for More Than One Cycle of Tabelecleucel....23
1.2.3.3 Rationale for Selection of Tabelecleucel Based on Human Leukocyte Antigen Restriction....23
1.2.3.4 Rationale for Switching the Tabelecleucel Human Leukocyte Antigen Restriction During Treatment....24
1.3 Nasopharyngeal Carcinoma and Rationale for Combination Therapy....25
2 OBJECTIVES....26
2.1 Primary Objectives....26
2.2 Secondary Objectives....26
2.3 Exploratory Objectives....26
3 INVESTIGATIONAL PLAN....27
3.1 Study Design....27
3.2 Endpoints....30
3.3 Study Stopping Criteria....31
3.4 Safety Data Review Committee....31
3.5 Dose and Dose De-escalation Plans....32
4 SELECTION AND WITHDRAWAL OF SUBJECTS....32
4.1 Number of Subjects....32
4.2 Eligibility Criteria....33
4.2.1 Inclusion Criteria....33
4.2.2 Exclusion Criteria....35
4.3 Contraception....37
4.4 Nursing Women....37
4.5 Meals and Dietary Restrictions....37
4.6 Subject Withdrawal Criteria....38

4.7 Subject Replacement 38
5 TREATMENT WITH INVESTIGATIONAL PRODUCT 38
5.1 Description of Investigational Products 38
5.1.1 Formulation 39
5.1.2 Packaging and Labeling 39
5.1.3 Storage and Handling 39
5.2 Administration of Investigational Products 39
5.2.1 Timing of Dose Administration 40
5.2.2 Duration of Treatment and Subject Participation 40
5.2.3 Definition of Dose-limiting Toxicity 41
5.2.4 Discontinuation of Treatment with Investigational Products after Complete Response 42
5.2.5 Dose Modifications 42
5.2.5.1 Dose Modification and Toxicity Management for Immune-related AEs associated with Pembrolizumab 42
5.2.5.2 Dose modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab 46
5.2.5.3 Other Allowed Dose Interruption for Pembrolizumab 47
5.2.5.4 Dose Modification for Tabelecleucel 48
5.2.5.5 Discontinuation of One Investigational Product 48
5.3 Prior and Concomitant Medications/Therapies 48
5.3.1 Permitted Medications/Therapies 48
5.3.1.1 Rescue Medications and Supportive Care 48
5.3.2 Prohibited Medications/Therapies 49
6 STUDY PROCEDURES 50
6.1 Inventory Check 50
6.2 Screening 50
6.3 Treatment/Consolidation Phase (21-day Cycles) 51
6.3.1 Treatment/Consolidation: Day 1 51
6.3.2 Treatment/Consolidation: Day 8 and Day 15 52
6.3.3 Treatment/Consolidation, Observation: Days 16 to 21 53
6.4 Maintenance Phase (84-day Cycles) 53
6.4.1 Maintenance: Day 1 53
6.4.2 Maintenance: Day 21, Day 42, and Day 63 54
6.4.3 Maintenance: Day 77 55
6.5 End-of-Treatment Visit 55
6.6 Quarterly Follow-up 56
6.7 Early Withdrawal 56
7 EFFICACY AND SAFETY ASSESSMENTS 56
7.1 Radiographic Tumor Assessments 56
7.1.1 Rationale for Endpoints Related to RECIST 57
7.1.2 Tumor Imaging and Assessment of Disease 57
7.1.2.1 Initial Tumor Imaging 58
7.1.2.2 Tumor Imaging During the Study 58
7.1.2.3 End-of-Treatment and Quarterly Follow-up Tumor Imaging 58
7.1.3 RECIST 1.1 Assessment of Disease 59

7.1.4 iRECIST Assessment of Disease 59
7.2 Laboratory Assessments 61
7.2.1 Local Laboratory Tests 61
7.2.2 Central Laboratory Tests 62
7.2.3 Reporting Routine Laboratory Abnormalities 63
8 ADVERSE EVENTS 63
8.1 Serious Adverse Events 64
8.1.1 Serious versus Severe Adverse Events 64
8.1.2 Serious Adverse Event Definition Clarifications 65
8.2 Adverse Events of Special Interest 65
8.2.1 Adverse Events of Special Interest for Pembrolizumab 65
8.2.2 Adverse Events of Special Interest and Possible Risks for Tabelecleucel 66
8.2.3 Treatment of Overdose 66
8.3 Severity (or Grading) of Adverse Events 67
8.4 Relationship of Adverse Events to Investigational Product 67
8.5 Adverse Event Reporting Requirements 68
8.5.1 Serious Adverse Event Reporting Requirements 68
8.5.2 Pregnancy Reporting Requirements 69
8.5.3 Investigator Reporting to the Institutional Review Board/Independent Ethics Committee 70
8.5.4 Sponsor Reporting Requirements 70
9 STATISTICS 71
9.1 Analysis Populations 71
9.2 Efficacy Analysis 71
9.3 Safety Analysis 71
9.4 CCI
9.5 Sample Size Determination 72
10 DATA COLLECTION, RETENTION, AND MONITORING 72
10.1 Data Collection and Retention 72
10.1.1 Data Collection Instruments 72
10.1.2 Data Management Procedures 72
10.1.3 Electronic Case Report Forms 72
10.1.4 Data Quality Control and Reporting 73
10.1.5 Archiving of Data 73
10.1.6 Source Document Maintenance 73
10.1.7 Investigational Product Accountability 73
10.2 Study Monitoring and Administrative Considerations 74
10.2.1 Study Monitoring 74
10.2.2 Documentation of Protocol Deviations 74
10.2.3 Study Completion 74
10.2.4 Audits and Inspections 75
10.2.5 Confidentiality 75
10.2.6 Financing and Insurance 76
10.2.7 Study Termination Criteria 76
11 ETHICS 76
11.1 Ethical Conduct of the Study 76

11.2 Ethics Review by the Institutional Review Board or Independent Ethics Committee 76
11.3 Informed Consent 77
12 INVESTIGATOR'S RESPONSIBILITIES 78
12.1 Study Reporting Requirements 78
12.2 Financial Disclosure and Obligations 78
12.3 Investigator Documentation 78
12.4 Institutional Review Board 79
12.5 Retention of Records 79
13 PUBLICATIONS 79
14 REFERENCES 80
15 APPENDIX 85
15.1 Schedule of Assessments and Procedures 85
15.2 Detailed of the Study Design 89
15.2.1 Complete or Partial Response after the Initial Two Treatment Cycles 89
15.2.2 Stable Disease after the Initial Two Treatment Cycles 89
15.2.3 Unconfirmed Progressive Disease after the Initial Two Treatment Cycles 90
15.2.4 Confirmed Progressive Disease after the Initial Two Treatment Cycles 91
15.3 Performance Status Scales 92
15.4 Corticosteroid Approximate Equivalent Doses 93
15.5 Description of the iRECIST Process for Assessment of Disease Progression 94
15.6 Severity Grading Scales 97
15.6.1 Acute GvHD 97
15.6.2 Chronic GvHD 98

List of Tables

Table 1 Comparison of the Concentration of Alloreactive and EBV-Specific T Cells in Unselected Donor Lymphocytes and In Vivo-Generated EBV-CTLs 23
Table 2 Dose Cohorts 28
Table 3 Initial Dose and Dose De-escalation Levels 28
Table 4 Investigational Products 39
Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab 43
Table 6 Pembrolizumab Infusion Reactions Dose modification and Treatment Guidelines 46
Table 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease 60
Table 8 CIBMTR Acute GvHD: Clinical Stage 97
Table 9 CIBMTR Acute GvHD: Severity Grading 98

List of Figures

Figure 1 Overall Study Design Schema (Cohorts 1 and 2).....29
Figure 2 Imaging and Treatment for Clinically Stable Subjects Treated with Tabelecleucel and Pembrolizumab after First Radiologic Evidence of Progressive Disease Assessed by the Investigator.....61

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
C	Celsius
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CTLp	cytotoxic T-lymphocyte precursor
DLT	dose-limiting toxicity-
DNA	deoxyribonucleic acid
DOiR	duration of immune response
CCI	CCI
EBV	Epstein-Barr virus
EBV-CTL	Epstein-Barr virus cytotoxic T lymphocyte
EBV-CTLp	EBV-specific cytotoxic T lymphocyte precursor
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FoxP3	forkhead box P3
GCP	Good Clinical Practice
CCI	CCI
GvHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematopoietic cell transplant

Abbreviation	Definition
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCR	immune complete response
IEC	Independent Ethics Committee
IFN γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
iPR	immune partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune response evaluation criteria in solid tumors
IRR	independent radiographic review
IV	intravenous(ly)
CCI	CCI
LPD	lymphoproliferative disorder
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NPC	nasopharyngeal carcinoma
NSAIDS	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD-1	programmed cell death protein-1
PD-L1, 2	programmed death-ligand1, 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	per os/by mouth

Abbreviation	Definition
PR	partial response
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disease
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SDRC	Safety Data Review Committee
SOT	solid organ transplant
SUSAR	serious unexpected suspected adverse reactions
T1DM	type 1 diabetes mellitus
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1 INTRODUCTION

1.1 Pharmaceutical and Therapeutic Background – Pembrolizumab

The importance of an intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [4]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation (CD)8^+ T cells and the ratio of $CD8^+$ effector T-cells/ forkhead box P3 (FoxP3)$^+$ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [9,17].

The programmed cell death protein-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T lymphocyte-associated protein-4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed death-ligand [PD-L]1 and/or PD-L2) [14,29].

The structure of murine PD-1 has been resolved [50]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, sarcoma homology 2 domain phosphatase-1 and -2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [29,5,41,34]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [30,10]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in Epstein-Barr virus-associated nasopharyngeal carcinoma (EBV^+ NPC; also referred to as NPC in this protocol).

1.1.1 Preclinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific $CD8^+$ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [3,6,16,32,42,43,48]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [7,26,36,39,43]. In such studies,

tumor infiltration by $CD8^+$ T cells and increased interferon-gamma (IFN-γ), granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo [7]. Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (refer to the pembrolizumab [MK-3475] Investigator's Brochure).

1.1.2 Pembrolizumab Background and Clinical Studies

Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the pembrolizumab (MK-3475) Investigator's Brochure.

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

1.1.3 Justification for Pembrolizumab Dose

1.1.3.1 Rationale for Pembrolizumab Adult Dose Selection

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W; ie during the 21-day treatment cycle). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by the following:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including overall survival (OS) at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2,262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold

difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

1.1.3.2 Rationale for Pembrolizumab Pediatric Dose Selection

To date, pembrolizumab (2 mg/kg Q3W) has been evaluated in 85 pediatric subjects (aged 1 to 18 years) with advanced melanoma, PD-L1 positive advanced, relapsed, or refractory solid tumors, or lymphoma. The exposures in pediatric subjects following the 2 mg/kg Q3W regimen were found to be similar to that observed in adult subjects. Pediatric data has also been incorporated in an integrated population PK analysis, which confirmed that a pembrolizumab dose of 2 mg/kg Q3W (up to a maximum of 200 mg Q3W) in pediatric subjects renders exposures similar to adults. Based on these results, the pediatric dose for evaluation in this study is 2 mg/kg Q3W (up to a maximum of 200 mg Q3W).

1.2 Pharmaceutical and Therapeutic Background – Tabelecleucel

For detailed background information, refer to the tabelecleucel (ATA129) Investigator's Brochure.

1.2.1 Tabelecleucel and Epstein-Barr virus-specific cytotoxic T lymphocytes

Atara Biotherapeutics, Inc. is developing tabelecleucel (ATA129; allogeneic EBV-specific cytotoxic T lymphocytes [EBV-CTLs]). EBV-CTLs (including tabelecleucel) for the treatment of EBV-associated lymphoproliferative disorders (LPD)/lymphoma, post-transplant lymphoproliferative disease (PTLD), and NPC in clinical studies have been generated from high-resolution human leukocyte antigen (HLA)-typed, EBV^+, related and unrelated primary stem cell donors. As for tabelecleucel, T cells from these donors are sensitized with autologous irradiated EBV-transformed B cells. The T cells are co-cultured with EBV-transformed

B lymphoblasts for 28 to 35 days with cytokine stimulation, and then characterized and cryopreserved for future use as a readily available T-cell immunotherapy [8].

1.2.2 Clinical Experience with Tabelecleucel for EBV+ PTLD

The clinical experience of tabelecleucel includes 5 clinical studies in subjects with EBV^+ PTLD following allogeneic hematopoietic cell transplant (HCT) or solid organ transplant (SOT); for details refer to the current edition of the tabelecleucel (ATA129) Investigator's Brochure. Safety results (from a 23 September 2017 analysis) of all 173 subjects treated in clinical studies and 15 patients treated through expanded access show tabelecleucel to have a favorable benefit-risk profile in subjects with rituximab refractory EBV^+ PTLD. Efficacy results (01 June 2017 analysis) of the clinical studies of patients with rituximab refractory EBV^+ PTLD have shown that tabelecleucel provides meaningful improvement in response rate and OS compared with currently available therapies and a favorable safety profile. Subjects with rituximab resistant, EBV^+ PTLD following allogeneic HCT (N = 35) had a response rate of 65.7% and a 1-year OS of 69.5% (with a median on-study follow-up time of 12.0 months), which exceed the response rate of 0% reported for CHOP administration and median survival of 16 to 56 days, as reported in the literature [10,28,38,46]. In subjects with EBV^+ PTLD following SOT (N = 14), the response rate was 50.0% and 1-year OS was 63.5%.

1.2.3 Justification for Dose

1.2.3.1 Dose Selection

For dose selection, tabelecleucel has been evaluated in 2 studies (95-024 and 11-130) for the treatment of EBV^+ LPDs or malignancies. In Study 95-024, the dose of tabelecleucel initially employed was 1×10^6 T cells/kg/dose weekly for 3 weeks followed by a 3-week period of observation. This dose provided a high effector EBV-CTL exposure while potentially co-transferring a cumulative dose of alloreactive cytotoxic T-lymphocyte precursors (CTLp) well below the threshold dose of 10^5 CTLp/kg, which was established for graft-versus-host disease (GvHD) in HLA-matched recipients [24] and the 0.5×10^4 CTLp/kg dose that has been associated with < 8% grade 2 acute GvHD or chronic GvHD after HLA non-identical transplants [27]. The number of EBV-specific CTL precursor (EBV-CTLp) and alloreactive CTLp detected in tabelecleucel administered to subjects in Study 95-024 are summarized in Table 1 and compared to doses that would be given were the subject to receive unselected donor lymphocytes. In this study, no recipient of tabelecleucel developed grade ≥ 2 acute GvHD or chronic GvHD; one subject developed a transient grade 1 skin rash, which cleared with topical steroid administration.

Table 1 Comparison of the Concentration of Alloreactive and EBV-Specific T Cells in Unselected Donor Lymphocytes and In Vivo-Generated EBV-CTLs

	EBV-CTLs Median (range), N=19	Unselected Donor Lymphocytes Median (range), N=5
EBV-Specific: EBV-CTLp concentration /10^6 T cells	1156 (66–6578)	17 (5.7–33)
Alloreactive: CTLp concentration /10^6 T cells	5.6 (< 1.28–29)	97 (2.8–223)
Grade ≥ 2 de novo acute GvHD and de novo chronic risk; 10^6 cells/kg in HLA-matched recipients	0%	32%

Abbreviations: EBV: Epstein-Barr virus; CTL: cytotoxic T lymphocyte; CTLp: CTL precursor; GvHD: graft-versus-host disease; HLA: human leukocyte antigen
Source: Prockop et al [33]

Because the dose of potentially reactive T cells was so low and no instance of acute grade ≥ 2 GvHD had been recorded, the dose of tabelecleucel was increased to 2×10^6 cells/kg/dose for Study 11-130. The results from Study 11-130 showed a higher response rate (RR), higher proportion of long-term survivors, and no added toxicity compared with data from Study 95-024. These results support the selection of a tabelecleucel dose of 2×10^6 cells/kg/dose for the current study.

1.2.3.2 Rationale for More Than One Cycle of Tabelecleucel

Studies have shown that in subjects with EBV^+ PTLD following allogeneic HCT, tabelecleucel were usually cleared within 4 weeks, and were never detected beyond day 90 following the first infusion [14]. In Studies 95-024 and 11-130, increments in the frequencies of EBV-CTLp have been detected after each course but have persisted for no more than 2 to 4 weeks [1,8]. Because NPC subjects are not as immunosuppressed as subjects who have received an allogeneic HCT, tabelecleucel is expected to be cleared more rapidly and multiple cycles of tabelecleucel are recommended, including maintenance therapy for those achieving disease control.

In subjects with NPC, the endogenous immune system is expected to eventually reject the partially HLA-matched tabelecleucel. Therefore, multiple administrations of tabelecleucel are expected to be required to optimize response.

1.2.3.3 Rationale for Selection of Tabelecleucel Based on Human Leukocyte Antigen Restriction

The rationale for selecting tabelecleucel cell products that are specifically restricted by an HLA allele shared by the subject and the tabelecleucel product are from findings reported from the first 19 subjects treated on Study 95-024 [8]. Specifically, tabelecleucel derived from an HLA haplotype disparate donor restricted by HLA was ineffective in a subject with an EBV^+ lymphoma because the subject and his tumor did not share the HLA allele. Subsequent treatment of the subject with tabelecleucel restricted by an HLA allele shared by the subject led to a complete remission of disease that has been durable to the present day, over 5 years later.

These data illustrate that administration of a tabelecleucel cell product matched via a restricting HLA allele shared on the subject's NPC tumor is required for product efficacy.

Clinical experience with tabelecleucel including a summary of safety is described in the tabelecleucel (ATA129) Investigator's Brochure.

1.2.3.4 Rationale for Switching the Tabelecleucel Human Leukocyte Antigen Restriction During Treatment

The rationale to switch tabelecleucel to a different shared HLA restriction in subjects who have not achieved a partial response (PR) or complete response (CR) after an initial course of tabelecleucel derives from Study 95-024 [8]. In 3 subjects with an EBV^+ lymphoma following allogeneic HCT who received tabelecleucel derived from the allogeneic HCT donor, the lymphoma was genetically shown to be of donor origin, and the tabelecleucel T cells generated from the donor by sensitization in vitro with autologous B cells transformed by the B95.8 EBV strain (different from the subject's EBV^+ lymphoma), were unable to lyse an endogenous EBV^+ B-cell line generated from the subject's lymphoma. The fact that the tabelecleucel T cells from the donor that were sensitized with the endogenous EBV^+ B-cell line grown from the subject could lyse the EBV^+ B-cell line and also lyse B cells transformed by the B95.8 EBV strain provided evidence that the endogenous EBV strain inducing the lymphoma lacked an antigen targeted by the tabelecleucel T cells sensitized with the B95.8 EBV transformed B cells rather than any defect in antigen processing or presentation of EBV antigens by the endogenous EBV^+ B-cell line. In a similar case of a subject who failed treatment, donor-derived T cells sensitized with an autologous EBV B95.8 transformed B-cell line were unable to lyse the EBV^+ tumor cells of the subject due to a mutation in the endogenous strain of EBV that resulted in deletion of two EBV-specific peptides presented by a specific HLA that were exclusively targeted by the donor-derived T cells used for treatment [13].

Based on these findings in Study 11-130, it was hypothesized that selection of an alternate tabelecleucel cell product restricted by a different HLA allele and therefore likely specific for a different EBV epitope expressed by the subject's lymphoma might prove effective given the low probability that the second epitope would also be mutated or deleted. Eight allogeneic HCT recipients underwent Switch Therapy with tabelecleucel from a different donor, restricted by a different HLA allele shared by the subject's disease; of the 8 subjects, 4 achieved CR and 1 achieved a durable PR. As with the infusions of tabelecleucel with the initial HLA restriction, no toxicities were observed following the infusions of tabelecleucel with a different HLA restriction. In one of these cases, the investigators were also able to isolate spontaneously transformed B cells from the subject's EBV^+ lymphoma. These B cells, bearing the endogenous strain of EBV, were not lysed by T cells from donors that were restricted by one HLA allele and had failed to arrest progression of disease, but were lysed by T cells from a tertiary donor that were restricted by another HLA allele.

While these findings support the hypothesis that Switch Therapy may lead to further lymphoma response and are being further evaluated in ongoing phase 3 studies in lymphoma; it is expected that a similar benefit may be observed in NPC as well. Hence, these findings support selecting an

alternative HLA restricted tabelecleucel cell product in subjects who fail to respond to tabelecleucel initially used for treatment.

1.3 Nasopharyngeal Carcinoma and Rationale for Combination Therapy

NPC is an undifferentiated squamous cell carcinoma with a worldwide incidence of approximately 80,000 new cases per year. NPC has an incidence of approximately one new case per year per 100,000 in the United States with children ≤ 16 years of age comprising about 10% of cases [1] and is endemic in southeast Asia with an incidence approximately 30 times higher. The World Health Organization classifies NPC as 3 types. The type 2b (III) nonkeratinizing undifferentiated form is the most common and is most strongly associated with EBV infection of the cancerous cells. Despite improvements in first-line and second-line treatments, advanced NPC has a poor prognosis. High-risk features include a Stage of IIb or higher, age greater than 50 years, EBV viremia, and high expression of PD-L1. The most commonly used treatments for head and neck cancers are platinum agents, taxanes, 5-fluorouracil, methotrexate and cetuximab; similar therapies are used for children. Subjects with low-stage disease have a 94% disease-free survival rate, while the rate is 38% to 80% for those with high-stage disease. Five-year survival is 80% (Stage I and II), 62% (Stage III), and < 10% (Stage IV).

The association between NPC and EBV is well known. EBV infection induces the expression of immunogenic peptides on the membrane of infected cells, and these virus-related antigens may be used as targets for antitumor immunotherapy-based treatment strategies [21].

The potential of autologous EBV-directed T-cell immunotherapy for NPC has been shown in several recent clinical studies. However, as it is not possible to generate autologous EBV-CTLs from all subjects, the use of EBV-directed immunotherapy with tabelecleucel has been investigated. Prockop et al [34] treated 14 subjects with metastatic EBV-associated NPC with tabelecleucel selected from a bank of more than 300 lines generated from EBV^+ HCT donors by sensitization of T cells with irradiated EBV-transformed B-cell lines. Cells were administered in cycles of 3 weekly doses of 1 to 2 x 10^6 cells/kg for a median of 2 cycles (range: 1 to 4 cycles). The results of this study showed that tabelecleucel has sufficient diversity to treat non-Caucasian subjects with NPC. Nine subjects were Asian, 3 were black, and 1 was Hispanic. Subjects had progressed after first (N=6) second (N=7) or third (N=1) line therapy. Tabelecleucel infusions were well tolerated without toxicities. One subject achieved a CR (documented by biopsy); lasting 21.2 months, 2 PRs lasting 3.5 and 6.7 months and one subject had stable disease (SD) lasting 7.4 months. All 4 subjects who achieved CR, PR or SD were alive at 20.4 to 48.3 months post therapy, and 11 subjects were alive at a median of 18.1 months (range: 3.0 to 48.4 months) after start of immunotherapy.

Given the minimal toxicities and ready availability, use of tabelecleucel for treatment of NPC is a promising option for combination with other therapies, such as PD-1/PD-L1 inhibition. Pembrolizumab is a PD-L1 inhibitor with a demonstrated objective response rate (ORR) of 25.9% amongst 27 subjects with advanced, unresectable NPC which demonstrated ≥ 1% PD-L1 expression in tumor using immunohistochemistry (IHC) analysis [18]; however, despite this, a proportion of subjects do not respond, and some responders relapse after immunotherapy. Exhaustion of the subject's own endogenous T-cell response is a potential contributing factor,

and in these cases, it is hypothesized that introduction of tabelecleucel will help to enable or recapture the previously lost immune response. Like tabelecleucel, pembrolizumab appears well tolerated in subjects with NPC based on available data [18]. Therefore, the current study will evaluate the combination tabelecleucel and pembrolizumab in subjects with NPC.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are:

- Phase 1B: To characterize the incidence of dose-limiting toxicities (DLTs) of tabelecleucel in combination with pembrolizumab in subjects with platinum-pretreated, recurrent/metastatic NPC
- To identify the maximum tolerated dose (MTD), or in the absence of an MTD, the recommended phase 2 dose (RP2D) of tabelecleucel when administered in combination with pembrolizumab
- Phase 2: To evaluate the objective response rate (ORR), defined as a CR or PR confirmed ≥ 28 days from the initial response assessment showing a response obtained following administration of the combination of tabelecleucel and pembrolizumab, where the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response is determined using an independent radiographic review (IRR)
- For both phase 1B and phase 2: To characterize the safety profile of tabelecleucel in combination with pembrolizumab in the NPC subject population

2.2 Secondary Objectives

The secondary objectives are as follows:

- To evaluate additional clinically relevant outcomes in subjects with NPC treated with tabelecleucel in combination with pembrolizumab, as measured by CR rate, duration of response (DOR; ie, CR + PR), progression-free survival (PFS) and OS
- To evaluate the immune response rate (iRR; ie, immune CR [iCR] + immune PR [iPR] rate) and duration of immune response (DOiR)

2.3 Exploratory Objectives

The exploratory objectives are as follows:

CCI

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is a multicenter, open-label, single-arm study in subjects with platinum-pretreated, recurrent/metastatic EBV+ NPC (also referred to as NPC in this protocol). The study will be conducted in 2 parts: Cohort 1 will be enrolled as the phase 1B portion to determine the phase 2 dose; Cohort 2 will be enrolled as the phase 2 portion to examine the clinical benefits of combined T cell and checkpoint inhibitor immunotherapies for the treatment of subjects with NPC. The study will enroll 48 to 60 subjects in total. Phase 1B (Cohort 1) will enroll 12 to 24 subjects. For each dose level explored in Cohort 1, at least 6 subjects must have had disease that is refractory to PD-1 or PD-L1 monoclonal antibody. All other subjects enrolled to Cohort 1 will be checkpoint inhibitor naïve subjects (have never received pembrolizumab or other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 [CD134] or anti-CTLA-4 products). Dose de-escalation is permitted in Cohort 1 only. Cohort 2 will enroll 36 subjects who are checkpoint inhibitor naïve.

Tabelecleucel will be selected for each subject from the bank of available tabelecleucel cell products based on matching ≥ 2 HLA alleles, at least one of which is a restricting HLA allele, ie, shared between the tabelecleucel source material (donor) and the subject.

The overall treatment schema is shown in Figure 1 and the planned dose cohorts are provided in Table 2. In Cohort 1, tabelecleucel will be administered initially to 12 subjects at a dose of 2×10^6 cells/kg IV on Day 1, Day 8, and Day 15 of a 21-day cycle. Pembrolizumab will be administered to adult subjects (≥ 18 years of age) at a dose of 200 mg IV Q3W (ie, on Day 1 of each 21-day cycle) and to pediatric (adolescent) subjects (12 to < 18 years of age) at a dose of 2 mg/kg IV Q3W. If ≥ 2 of the initial 6, or ≥ 4 of the initial 12, Cohort 1 subjects experience a DLT in the first 21 days, the dose of tabelecleucel will be reduced to 1×10^6 cells/kg/dose, and an additional 12 subjects will be treated with the combination of tabelecleucel at 1×10^6 cells/kg/dose and pembrolizumab at the recommended dose level (Table 3). Otherwise,

all 12 subjects in Cohort 1 will receive tabelecleucel at 2 x 10^6 cells/kg/dose and pembrolizumab at the recommended dose level.

A Safety Data Review Committee (SDRC) composed of representatives from the sponsor and the principal investigators or designated sub-investigators from all sites enrolling subjects in Cohort 1 will review reported DLTs and cumulative safety data to determine further enrollment. The data review will occur as soon as possible after Cycle 1 Day 21 of the last subject in Cohort 1. After the SDRC review, 36 subjects will be enrolled in Cohort 2 and treated with the combination at the recommended dose level.

Table 2 Dose Cohorts

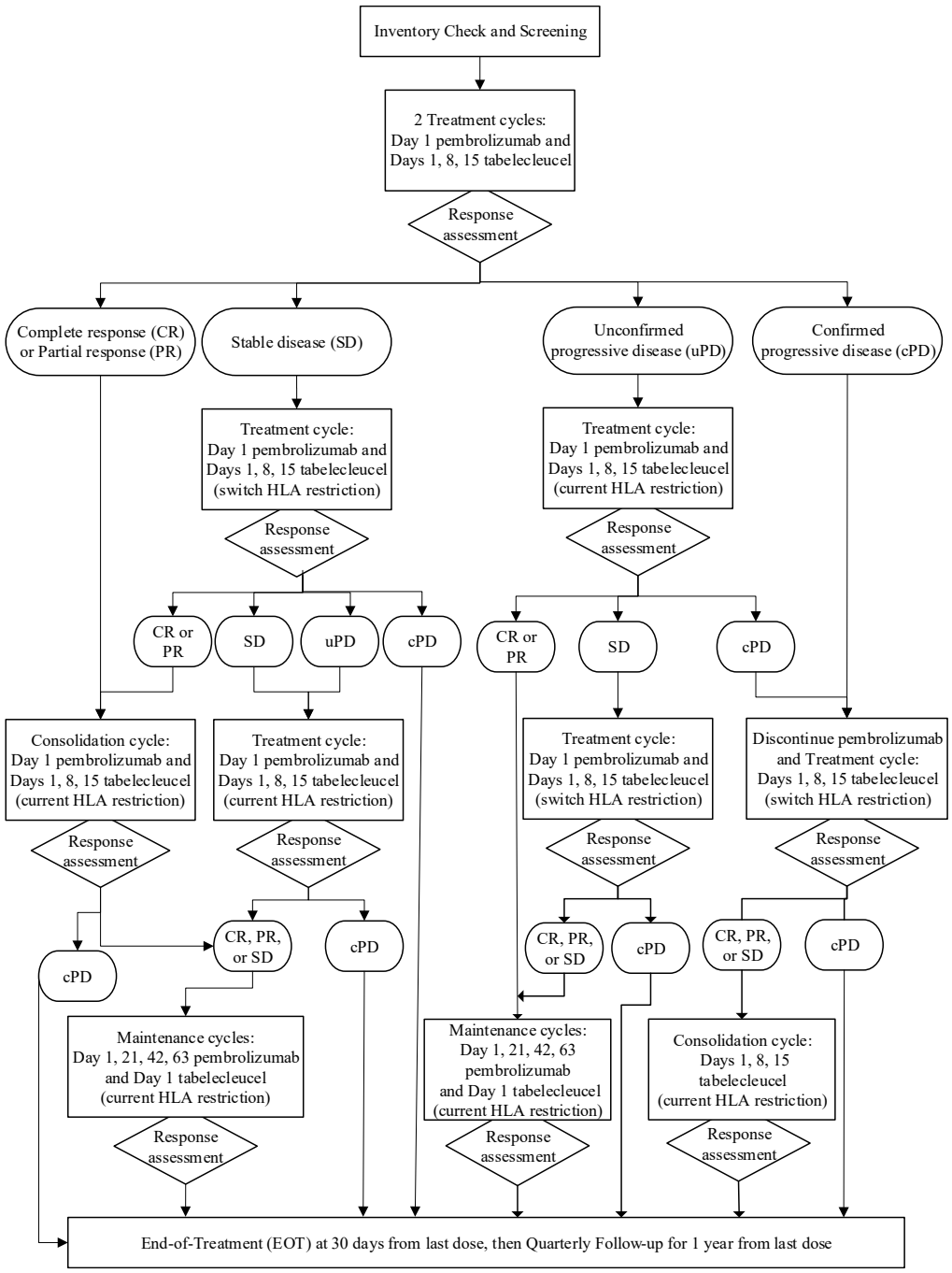
Cohort	Number of Subjects	Prior Therapy
1	12 to 24	Checkpoint inhibitor naïve [a] or PD-1/PD-L1 failures (ie, refractory to or relapsed after PD-1/PD-L1 treatment) At least 6 of the 12 subjects must have disease that is refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody for each dose level explored
2	36	Checkpoint inhibitor naïve [a] subjects

[a] Checkpoint inhibitor naïve have never received pembrolizumab or other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies

Table 3 Initial Dose and Dose De-escalation Levels

	Tabelecleucel Dose (cells/kg)	Pembrolizumab Adult Dose (mg)	Pembrolizumab Pediatric Dose (mg/kg)
Dose level 1	2×10^6 on Day 1, Day 8 and Day 15	200 on Day 1	2 on Day 1
Dose level 2	1×10^6 on Day 1, Day 8 and Day 15	200 on Day 1	2 on Day 1

Figure 1 Overall Study Design Schema (Cohorts 1 and 2)



NOTE: A maximum of 4 treatment/consolidation cycles and 1 switch of tabelecleucel to a different HLA restriction (Switch Therapy) is permitted if an appropriately matched product is available.

* For a clinically stable subject with first radiographic evidence of progressive disease by RECIST 1.1 (ie, unconfirmed PD [uPD]), it is at the discretion of the investigator not continue treating the subject with the assigned treatment per protocol until cPD at least 28 days from the date of the scan first suggesting progressive disease. If radiographic progression is not confirmed by immune (i)RECIST per the investigator, then the subject may continue on treatment as described above in consultation with the sponsor's medical monitor.

During the Treatment Phase, subjects will receive two 21-day treatment cycles of combination immunotherapy and then undergo a response assessment at the Observation Visit (refer to Figure 1). Based on the subject's response to the initial 2 cycles s/he may receive one additional consolidation cycle with the same tabelecleucel product or additional treatment cycles with tabelecleucel with the same or a different HLA restriction, if an appropriately matched product is available. Detailed descriptions are provided in Section 15.2. At any time during the Treatment Phase if a subject has a confirmed progressive disease (cPD), it is at the investigator's discretion to continue treatment with tabelecleucel with a different HLA restriction (Switch Therapy), if available without pembrolizumab. A maximum of 4 treatment/consolidation cycles and 1 Switch Therapy, if available will be permitted.

During the Maintenance Phase, subjects will receive tabelecleucel on Day 1 and pembrolizumab on Day 1, Day 21, Day 42, and Day 63 of 84-day maintenance cycles, which will continue until disease progression, unacceptable toxicity, or a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given. After completing the End-of-Treatment (EOT) Visit 30 days after the last dose of investigational product, subjects will enter quarterly follow-up until 12 months after the last dose of investigational product or until disease progression. During this last phase, survival and disease status will be collected. The end-of-study is defined as the date of the last quarterly follow-up.

3.2 Endpoints

The primary endpoints are:

- The incidence of DLTs in Cohort 1
- The MTD, or in the absence of an MTD the RP2D, of tabelecleucel when administered in combination with pembrolizumab
- The ORR of tabelecleucel in combination with pembrolizumab
- The characterization of the safety profile of tabelecleucel in combination with pembrolizumab in subjects with NPC

Secondary endpoints are:

- CR rate, DOR, PFS, and OS
- iRR (ie, iCR + iPR rate) and DOiR

Exploratory endpoints are:

CCI

3.3 Study Stopping Criteria

This study includes the following design elements to reduce risk to subjects:

- Dose de-escalation based on the number of DLTs experienced; DLTs are described in Section 5.2.3
- Cohort review: all Cohort 1 data will be reviewed by the SDRC prior to beginning enrollment of Cohort 2
- DLT review: when a DLT is reported, the event is reviewed within the context of all treated subjects and available study data

The sponsor may suspend treatment and/or enrollment to assess risk based on any of the following:

- Number of DLTs experienced as described in Section 5.2.3
- Identification of a significant safety signal that requires time for further assessment

Depending on the outcome of these reviews, the sponsor may amend the protocol or stop the study.

3.4 Safety Data Review Committee

A SDRC composed of representatives from the sponsor and the principal investigators or designated sub-investigators from all sites enrolling subjects in Cohort 1 will review reported DLTs and cumulative safety data to determine further enrollment. The data review will occur as soon as possible after Cycle 1 Day 21 of the last subject in Cohort 1.

The sponsor's medical monitor and global safety officer will review data on an ongoing basis and may suspend dosing and/or enrollment and convene a SDRC meeting at any time based on emerging safety data.

3.5 Dose and Dose De-escalation Plans

The study dose and dose de-escalation plans, which will include applicable review(s) by the SDRC (Section 3.4), is described as follows:

- At the 2×10^6 dose level:
  - If ≤ 1 of the first 6 subjects in Cohort 1 experiences DLTs, the next 6 subjects will be enrolled in Cohort 1 at the 2×10^6 dose level.
    - If ≤ 3 of the 12 total subjects in Cohort 1 experience DLTs, Cohort 2 will proceed with enrollment of 36 subjects at the 2×10^6 dose level.
  - If ≥ 2 of the first 6 subjects experience DLTs, the dose will be de-escalated to 1×10^6, and the next 6 subjects will be enrolled in Cohort 1 at the lower dose level of 1×10^6. Continue with the steps for the 1×10^6 dose level.
    - If ≥ 4 of the 12 total subjects experience DLTs, the dose will be de-escalated to 1×10^6 and the next 6 subjects will be enrolled in Cohort 1 at the lower dose level of 1×10^6. Continue with the steps for the 1 x 10^6 dose level.
- At the 1×10^6 dose level:
  - If ≤ 1 of the first 6 subjects experiences DLTs, the next 6 subjects will be enrolled in Cohort 1 at the 1×10^6 dose level.
    - If ≤ 3 of the 12 total subjects in Cohort 1 experience DLTs, Cohort 2 will proceed with enrollment of 36 subjects at the 1×10^6 dose level.
  - If ≥ 2 of the first 6 subjects or > 4 of the 12 total subjects experience DLTs, all further enrollment will be stopped and continued dosing of current subjects receiving active treatment will be evaluated by SDRC for an individual benefit-risk assessment.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Number of Subjects

Up to a total of 48 to 60 subjects will be enrolled in the study. The phase 1B portion (Cohort 1) of the study will enroll 12 to 24 subjects. For each dose level explored in Cohort 1, at least 6 subjects must have disease that is refractory to a PD-1 or PD-L1 monoclonal antibody. The other subjects enrolled to Cohort 1 will be checkpoint inhibitor naïve subjects (have never received pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies). The phase 2 portion (Cohort 2) of the study will enroll 36 subjects who are checkpoint inhibitor naïve.

4.2 Eligibility Criteria

Subjects must undergo a tabelecleucel inventory check to ensure availability of an appropriately matched and restricted tabelecleucel cell product prior to undergoing screening procedures. The inventory check includes collection of the subject's high-resolution HLA typing (DNA-based versus serologic assessment) and weight.

Investigators may submit de-identified information (ie, historically available high-resolution HLA typing and current weight) for potential subjects being referred from outside institutions (as long as the referring physician has documented in the potential subject's chart that s/he was notified that their data was being sent through a study investigator to Atara Biotherapeutics, Inc. and that the potential subject consented for this to be done). This de-identified information will be used to determine whether an appropriately HLA-matched product is available to warrant a referral to the study site for potential study participation.

4.2.1 Inclusion Criteria

A subject will be considered eligible to participate in this study if all of the following inclusion criteria are satisfied:

1. Male or female ≥ 12 years of age
2. Incurable, locally recurrent or metastatic NPC (World Health Organization type II/III) in whom the EBV nucleic acid or antigens have been demonstrated in tissue biopsy samples
3. Subjects must have had prior receipt of platinum-containing regimen, ***either***:
   a. For the treatment of recurrent or metastatic disease, ***or***
   b. Experienced progression of disease within 6 months following completion of a platinum-based combination therapy as part of (neo)adjuvant chemotherapy. Note: Patients who had only concurrent chemoradiation therapy without (neo)adjuvant therapy and then recurred/metastasized must have progressed on at least 1 platinum-containing regimen for their recurrent/metastatic disease before study entry.
4. Phase 1B (Cohort 1):
   a. Checkpoint inhibitor naïve (have never received pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies)

   OR

   b. Refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody approved by the local regulatory agency either as monotherapy or in combination with other checkpoint inhibitors or therapies according to their approved label. To be considered refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody, all of the following criteria must be met:
      i. Received at least 2 doses of anti-PD-1 or anti-PD-L1 monoclonal antibody at a local regulatory agency-approved dose and schedule.

ii. Have progressive disease after anti-PD-1 or anti-PD-L1 monoclonal antibody as defined according to RECIST 1.1. The initial evidence of progressive disease is to be confirmed by a second assessment, no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression. (The eligibility determination will be made by the investigator and then the sponsor will collect for retrospective analysis at a central vendor. Once progressive disease is confirmed, the initial date of progressive disease documentation will be considered the date of disease progression).

iii. Documented disease progression within 24 weeks of the last dose of anti-PD-1 or anti-PD-L1 monoclonal antibody. A subject who was re-treated with anti-PD-1 or anti-PD-L1 monoclonal antibody and a subject who was on maintenance with an anti-PD-1 or anti-PD-L1 monoclonal antibody will be allowed to enter the study as long as there is documented PD within 24 weeks of the last treatment date (with the anti-PD-1 or anti-PD-L1 monoclonal antibody).

5. Phase 1B (Cohort 1): If PD-1/PD-L1 failure (ie, refractory to or relapsed after PD-1/PD-L1 treatment), must have a lesion that can be biopsied after administration of tabelecleucel with acceptable clinical risk (as judged by the investigator) and must agree to undergo biopsy before Cycle 1 Day 1
6. Phase 2 (Cohort 2): Checkpoint inhibitor naïve (have never received pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX40 or anti-CTLA-4 antibodies)

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8. Life expectancy ≥ 4 months at time of screening
9. Measurable disease using RECIST 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been documented in such lesions.
10. Eastern Cooperative Oncology Group (ECOG) performance status of < 2 for subjects aged > 16 years; Lansky score ≥ 70 for subjects aged 12 to 16 years (refer to Section 15.2)
11. Adequate organ function per the following:

System	Laboratory Value
Hematological	
ANC	≥ 1,500/µL
Platelets	≥ 100,000/µL
Hemoglobin[a]	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated creatinine clearance[b] (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x ULN **OR** ≥ 30 mL/min for subject with creatinine levels > 1.5 x ULN

System	Laboratory Value
Hepatic	
TBILI	≤ 1.5x ULN **OR** Direct bilirubin ≤ ULN for subjects with TBILI > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN ≤ 5 x ULN for subjects with liver metastases
Coagulation	
INR or PT aPTT	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance should be calculated per institutional standard.

12. Willing and able to provide written informed consent (pediatric subjects 12 to < 18 years of age must provide assent along with consent from the subject's legally authorized representative)

4.2.2 Exclusion Criteria

A subject will not be eligible to participate in the study if any of the following criteria are met:

1. Disease that is suitable for local therapy administered with curative intent
2. Receives vasopressor or ventilator support
3. Received antithymocyte globulin or similar anti-T cell antibody therapy ≤ 4 weeks prior to Cycle 1 Day 1
4. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to Cycle 1 Day 1of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor's medical monitor.
5. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
6. History or evidence of interstitial lung disease
7. History of severe hypersensitivity (Grade ≥ 3) to pembrolizumab and/or any of its excipients
8. Active infection requiring systemic therapy

9. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
10. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor or recombinant erythropoietin) within 4 weeks prior to study Day 1
11. Unresolved immunotherapy-related AEs or treatment for these events within 4 weeks prior to enrollment
12. History of severe immunotherapy-related adverse effects (Common Terminology Criteria for Adverse Events [CTCAE] grade 4 or CTCAE grade 3 requiring treatment > 4 weeks)
13. Received any non-oncology vaccine therapy used for prevention of infectious diseases for up to 30 days prior to enrollment. Examples include, but are not limited to: measures, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are acceptable.
14. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
15. Pregnancy or breastfeeding; females of childbearing potential must have a negative serum pregnancy test. The serum pregnancy must be confirmed negative within 72 hours of Cycle 1 Day 1 (first dose of investigational product) for the subject to be eligible.
16. Female of childbearing potential or male with a female partner of childbearing potential unwilling to use a highly effective method of contraception (abstinence is acceptable) for the course of the study through 120 days after the last study dose.
17. Inability to comply with study procedures
18. Received chemotherapy or targeted small molecule therapy within 2 weeks of Cycle 1 Day 1. Subjects must have recovered (ie, grade ≤ 1 or at baseline) from AEs due to a previously administered agent. Subjects with grade ≤ 2 neuropathy or grade ≤ 2 alopecia are an exception to this criterion.
19. Received prior radiotherapy within 2 weeks of Cycle 1 Day 1. 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-central nervous system (CNS) disease.
20. Antibody/biologic therapy within 4 weeks of Cycle 1 Day 1 or not recovered (ie, grade ≤ 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier
21. Carcinomatous meningitis and/or active CNS metastases, unless metastases are treated and stable and the subject does not require systemic steroids NOTE: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either magnetic resonance imaging (MRI) or computed tomography (CT) scan] for at least four weeks prior to the first dose of investigational product 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 7 days prior to first dose of investigational product. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

22. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
23. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study
24. Known history of human immunodeficiency virus (HIV), known active hepatitis B virus (HBV; eg, hepatitis B surface antigen [HBsAg] reactive), or hepatitis C virus (HCV; eg, HCV ribonucleic acid [RNA] is detected)
25. Prior treatment with any investigational product within 4 weeks of Cycle 1 Day 1
26. Prior treatment with EBV T cells

4.3 Contraception

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

Females of childbearing potential and males with a female partner of childbearing potential must be willing to use a highly effective method of contraception.

In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of investigational product initiation (or 14 days prior to the initiation of investigational product for oral contraception) throughout the study period up to 120 days after the last dose of investigational product. 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.

4.4 Nursing Women

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

4.5 Meals and Dietary Restrictions

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

4.6 Subject Withdrawal Criteria

A subject may withdraw either from (1) investigational product treatment only, in which case the subject will continue protocol defined follow-up assessments or (2) study participation, in which case investigational product and study assessments will be discontinued. Whenever possible, continue protocol-defined follow-up after the subject has discontinued investigational product treatment (refer to Section 6.7).

Investigational product treatment may be discontinued for any of the following reasons:

- Occurrence of an AE that precludes further treatment, refer to Section 5.2.5
- Achieves a sustained CR, refer to Section 5.2.4
- Receives a prohibited treatment, such as use of a different investigational product or non-protocol anti-NPC therapy
- Decision (by subject or investigator) that continued investigational product treatment is not in the subject's best interest

Study participation may be discontinued for any of the following reasons:

- Withdrawal of consent by subject or subject's legally authorized representative
- Early closure of the study by the sponsor
- Subject is lost to follow-up

4.7 Subject Replacement

Subjects who discontinue due to a DLT after receiving both pembrolizumab and tabelecleucel during the 21-day DLT assessment window will not be replaced; however, subjects who discontinue due to a DLT associated with the first infusion of pembrolizumab (ie, prior to any tabelecleucel infusion) will be replaced. Subjects who discontinue from Cohort 1 for any reason other than a DLT prior to completing the 21-day DLT assessment window will be replaced until the required number of evaluable subjects complete the 21-day DLT assessment window. Subjects will not be replaced in Cohort 2.

5 TREATMENT WITH INVESTIGATIONAL PRODUCT

5.1 Description of Investigational Products

The treatments to be used in this study are outlined below in Table 4.

Table 4 Investigational Products

Investigational Product Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Pembrolizumab	Solution for infusion	100 mg/vial	200 mg Q3W (adults, ≥ 18 years) 2 mg/kg Q3W (children, 12 to < 18 years)	IV infusion	Merck
Tabelecleucel	Sterile aqueous suspension	Up to 5×10^7 cells/mL	1 or 2×10^6 cells/kg	IV infusion	Atara

5.1.1 Formulation

Tabelecleucel is formulated as a sterile aqueous suspension intended for IV administration. The product contains 10% dimethyl sulfoxide, 15% human serum albumin, and buffered saline.

Pembrolizumab is provided as a sterile solution of 100 mg in 4 mL (25 mg/mL).

Refer to the Investigational Product Manual for details of dose preparation.

5.1.2 Packaging and Labeling

Tabelecleucel is supplied in single-use vials.

Pembrolizumab is supplied in a single-use vial for IV infusion.

5.1.3 Storage and Handling

Tabelecleucel will be shipped to study sites where it will be stored in a liquid nitrogen-charged canister until ready for dose preparation. To prepare the product for infusion, the frozen vial is to be thawed and the dose prepared as specified in the Investigational Product Manual. Once thawed, the product must be used immediately; the unused portion must not be refrozen or reused and must be discarded. The thawed product is to be handled or transported at ambient room temperature.

Pembrolizumab should be stored refrigerated at 2° to 8°C (36° to 46°F) and should not be frozen or shaken. Protect from light.

Refer to the Investigational Product Manual for detailed instructions for storage and handling of the products.

5.2 Administration of Investigational Products

A treatment/consolidation cycle in the Treatment Phase of the study will last 3 weeks (21 days) and consist of 1 dose of pembrolizumab administered on Day 1 and 3 doses of tabelecleucel administered on Day 1, Day 8 (± 2), and Day 15 (± 2) of each cycle; pembrolizumab will be administered approximately 1 hour before tabelecleucel.

During the Maintenance Phase of the study, a maintenance cycle will last 84 days. Subjects will receive pembrolizumab on Day 1, Day 21 (± 2), Day 42 (± 2), and Day 63 (±2) and tabelecleucel on Day 1 of each 84-day cycle; pembrolizumab will be administered approximately 1 hour before tabelecleucel.

Pembrolizumab: Pembrolizumab will be administered using IV infusion on Day 1 of the 21-day treatment/consolidation cycle after all procedures and assessments have been completed (except vital signs, which will be measured before and after all investigational product infusions).

Pembrolizumab will be administered as a dose of 200 mg (adults ≥ 18 years of age) or 2 mg/kg (children 12 to < 18 years of age) using a 30-minute IV infusion. Investigators should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from study site to site, a window between -5 minutes and +10 minutes is permitted, ie, infusion time is 30 minutes (-5 min/+10 min).

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

Tabelecleucel: Tabelecleucel will be selected for each subject from the bank of available tabelecleucel cell products based on matching ≥ 2 HLA alleles, at least one of which is a restricting HLA allele, shared between the tabelecleucel source material (donor) and the subject.

Tabelecleucel will be administered via a slow IV push over 5 to 10 minutes at a dose of 2×10^6 cells/kg body weight (the Cohort 1 de-escalation dose is 1.0×10^6 cells/kg) after all procedures and assessments have been completed (except vital signs, which will be measured before and after all investigational product infusions).

5.2.1 Timing of Dose Administration

On the study days in which both investigational products are administered (ie, Day 1 of treatment/consolidation cycles and Day 1 of maintenance cycles), tabelecleucel will be administered 1 hour (± 10 minutes) after the completion of pembrolizumab.

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (ie, elective surgery, unrelated medical events, subject vacation, holidays) not related to the administration of investigation product. Subjects should be placed back on the treatment schedule within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor's medical monitor. The reason for dose interruption should be documented in the subject's study record.

5.2.2 Duration of Treatment and Subject Participation

The duration of treatment is dependent on a subject's response to treatment and is estimated to be approximately 2 years for subjects with a response to treatment (CR, PR, or SD): a maximum of 4 treatment/consolidation cycles (21-day cycles of 3 infusions of tabelecleucel and 1 of pembrolizumab) and maintenance cycles (84-day cycles of 4 infusions of pembrolizumab and

1 of tabelecleucel) until up to a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given.

After treatment/consolidation and maintenance cycles, subjects will have an End-of-Treatment visit (30 days after the last dose of investigational product) and then enter Quarterly Follow-up for 12 months after the last dose of investigational product. Before receiving any treatment, subjects must undergo a tabelecleucel inventory check and screening, with screening up to 28 days prior to the first dose of investigational product.

5.2.3 Definition of Dose-limiting Toxicity

All toxicities will be graded based on the investigator's assessment using CTCAE version 5, except for certain events described in Section 8.3, which have a separate grading system.

The DLT window of observation will be during Treatment Cycle 1 only (ie, during the first 21-day cycle; adverse events (AEs) meeting the definition of a DLT but occurring after this period will not be considered DLTs).

The occurrence of any of the following toxicities during Treatment Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly related or related to investigational product administration (either tabelecleucel and/or pembrolizumab), excluding toxicities clearly not related to the investigational product, such as disease progression, environmental factors, unrelated trauma, etc.:

- Grade 4 nonhematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia associated with bleeding that requires a platelet transfusion
- Any nonhematologic AE grade ≥ 3 in severity should be considered a DLT, with the following exceptions: grade 3 fatigue lasting ≤ 3 days; grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
- Any grade 3 or grade 4 non-hematologic laboratory value if:
  - Clinically significant medical intervention is required to treat the subject, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for > 1 week.
  - The abnormality results in a Drug-induced Liver Injury (DILI)
  - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

- Febrile neutropenia grade 3 or grade 4:
  - Grade 3 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour
  - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Missing > 25% of pembrolizumab or tabelecleucel doses as a result of investigational product-related AE(s) during the first cycle.
- Grade 5 toxicity.

Any subject experiencing any DLT will be withdrawn from treatment (both investigational products). Whenever possible, protocol-defined follow-up will be continued after the subject has discontinued investigational product treatment (refer to Section 6.7).

MTD definition: The MTD is defined as the highest dose level at which the subject incidence of a DLTs during the first 21-day cycle of investigational product dosing is < 33%.

RP2D definition: The RP2D is no higher than the MTD and is based on optimal benefit-risk, as determined by the SDRC.

5.2.4 Discontinuation of Treatment with Investigational Products after Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 6 weeks with tabelecleucel and 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab and 1 cycle tabelecleucel beyond the date when the initial CR was observed.

While subjects achieving a CR may discontinue treatment, they will not be considered to have discontinued the study unless consent is withdrawn. If study consent is not withdrawn the subject will complete an End-of-Treatment visit and enter in the Quarterly Follow-up Phase of the study.

5.2.5 Dose Modifications

5.2.5.1 Dose Modification and Toxicity Management for Immune-related AEs associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the

last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5, and refer to the approved label. See Section 5.3.1.1 for supportive care guidelines, including use of corticosteroids.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions:

Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAEs	**Toxicity grade or conditions**	**Action taken to pembrolizumab[a]**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold		

irAEs	**Toxicity grade or conditions**	**Action taken to pembrolizumab[a]**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Subjects with Grade ≥ 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased TBILI	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold		

irAEs	Toxicity grade or conditions	Action taken to pembrolizumab[a]	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3 or 4	Withhold or permanently discontinue	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

irAEs	Toxicity grade or conditions	Action taken to pembrolizumab[a]	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; irAE: immune-related AE; IV: intravenous(ly); T1DM: type 1 diabetes mellitus; TBILI: total bilirubin. NOTE: For subjects with Grade 3 or Grade 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to grade ≤ 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM). [a] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.				

5.2.5.2 Dose modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reactions are provided in Table 6.

Table 6 Pembrolizumab Infusion Reactions Dose modification and Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	**Stop Infusion**. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

Table 6 Pembrolizumab Infusion Reactions Dose modification and Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hour to 50 mL/hour). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	
Grade 3 or Grade 4 **Grade 3**: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4**: Life-threatening; pressor or ventilator support indicated	**Stop Infusion**. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further study drug treatment.	No subsequent dosing

Abbreviations: IV: intravenous(ly), NSAID: nonsteroidal anti-inflammatory drug, PO: per os/by mouth.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to CTCAE version 5.

5.2.5.3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment emergent related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor's medical monitor. The reason for dose interruption should be documented in the subject's study record.

5.2.5.4 Dose Modification for Tabelecleucel

If ≥ 2 of the initial 6, or ≥ 4 of the initial 12 Cohort 1 subjects experience a DLT in the first 21 days, the dose of tabelecleucel will be reduced to 1 x 10^6 cells/kg/dose, and the subsequent 12 subjects will be treated with the combination of tabelecleucel at 1 x 10^6 cells/kg/dose and pembrolizumab at the recommended dose level. Otherwise, all 12 subjects in Cohort 1 will receive tabelecleucel at 2 x 10^6 cells/kg/dose and pembrolizumab at the recommended dose level. An SDRC composed of representatives from the sponsor and the principal investigators or designated sub-investigators from all sites enrolling subjects in Cohort 1 will review reported DLTs and cumulative safety data to determine further enrollment. The data review will occur as soon as possible after Cycle 1 Day 21 of the last subject in Cohort 1. For additional details on dose stopping rules (refer to Section 3.3 for additional details).

5.2.5.5 Discontinuation of One Investigational Product

Upon approval by the medical monitor, a subject may continue to receive 1 investigational product if the other is withheld or discontinued for any reason other than due to a DLT observed during the first 21 days of combination treatment.

5.3 Prior and Concomitant Medications/Therapies

5.3.1 Permitted Medications/Therapies

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; however, refer to prohibited medications and therapies in Section 5.3.1.1. All concomitant medication will be recorded, including all prescription, over-the-counter, 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 recorded.

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before the first dose of investigational product and 30 days after the last dose of investigational product should be recorded. Concomitant medications administered after 30 days after the last dose of investigational product should be recorded if related to any serious AEs (SAEs) and AEs of special interest as defined in Section 8.2.

5.3.1.1 Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.5 (Table 5). Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral

infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

If a pembrolizumab-related toxicity requires > 0.5 mg/kg of prednisone equivalent, then tabelecleucel should be held until the steroids are tapered to below 0.5 mg/kg.

Note: If after the evaluation the event is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 5 in Section 5.2.5 for guidelines regarding dose modification and supportive care.

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

5.3.2 Prohibited Medications/Therapies

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 4.2.2) are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor's medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study therapy requires the mutual agreement of the investigator, the sponsor, and the subject.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational products other than pembrolizumab or tabelecleucel
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion
- Live vaccines within 30 days prior to the first dose of investigational product and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, bacille Calmette-Guerin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist®) 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's medical monitor.

– Note: Inhaled steroids are allowed for management of asthma.

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. 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.

There are no prohibited therapies during Quarterly Follow-up Phase.

6 STUDY PROCEDURES

Study assessments and procedures are tabulated in Section 15.2.

6.1 Inventory Check

Subjects must undergo a tabelecleucel inventory check to ensure availability of an appropriately matched and restricted tabelecleucel cell product prior to undergoing screening procedures.

Within 5 to 10 days prior to screening, the following *required* assessments/procedures will be collected or performed after consent is signed:

- Written informed consent by the subject or the subject's legally authorized representative
- High resolution HLA typing (HLA-A, -B, -C, -DRB1, -DQB1) of the subject
- Cytomegalovirus (CMV) antibody status (local laboratory)
- Demographics
- Subject weight
- AEs considered at least possibly related to study procedure(s) after first informed consent

NOTE: Subjects with historical high-resolution HLA typing may submit their data for this inventory check as described in Section 4.2.

6.2 Screening

Within 28 days prior to study enrollment (Cycle 1 Day 1), the following *required* assessments/procedures will be collected or performed after consent is signed, unless otherwise specified:

- Written informed consent by the subject or the subject's legally authorized representative
- Verification that subject meets all inclusion and exclusion criteria
- Complete medical history
- Physical examination
- Height and weight

- Performance status: ECOG for subjects > 16 years of age or Lansky score for subjects 12 to 16 years of age
- AEs considered at least possibly related to study procedure(s)
- Concomitant medications
- Vital signs (body temperature, blood pressure (BP), heart rate (HR), and respiratory rate)
- CCI [redacted]
- Radiographic assessments (MRI or CT with contrast) as described in Section 7.1
- CCI [redacted]
- Hematology panel: complete blood count (CBC) with platelet count and differential
- Coagulation panel: prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
- Full chemistry panel: sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose (fasting), total calcium, albumin, total protein, serum creatinine, total bilirubin (TBILI), ALT, AST, alkaline phosphatase, and tests of thyroid function (thyroid stimulating hormone [TSH], T3, and T4)
- **Cohort 1, checkpoint inhibitor (PD-1/PD-L1) failed subjects only:**
  - Tumor/active site biopsy or archival sample as described in Section 7.2 (central laboratory); hematology and coagulation panels must be performed prior to biopsy
  - Initial evidence of progressive disease with confirmation assessment retrospective analysis at a central vendor, refer to inclusion criterion 4.b.ii
- **Cohort 1, checkpoint inhibitor-naïve subjects, and Cohort 2:** Archival tumor block/tumor sections if available (central laboratory)

Within 72 hours prior to Cycle 1 Day 1, the following procedure will be performed:

- Pregnancy test for women of childbearing potential (serum)

6.3 Treatment/Consolidation Phase (21-day Cycles)

All subjects will receive 2 treatment cycles (21-day), and depending on their response to treatment, subjects may receive additional treatment and/or consolidation cycles (21-day), refer to Section 15.2. During treatment and consolidation cycles, subjects will receive tabelecleucel on Day 1, Day 8 (± 2), and Day 15 (± 2) and pembrolizumab on Day 1 and have a response assessment within 7 days after Cycle 2 Day 15 and every treatment/consolidation cycle thereafter.

6.3.1 Treatment/Consolidation: Day 1

- Physical examination including weight
- AEs

- Concomitant medications
- Hematology panel: CBC with platelet count and differential
- Abbreviated chemistry panel: serum creatinine, TBILI, ALT, AST, alkaline phosphatase, glucose (fasting) and tests of thyroid function (TSH, T3, and T4)
- **Cycle 1 and Cycle 2 only:** CCI [redacted]
- **Cycle 2 and subsequent cycles:** CCI [redacted]
- Investigational product infusions:
  - Pembrolizumab will be administered prior to tabelecleucel
  - Tabelecleucel will be administered 1 hour (± 10 minutes) after completion of the administration of pembrolizumab only if no infusion reactions related to pembrolizumab are observed/reported or in the case of such a reaction, the subject has recovered
- Vital signs (body temperature, BP, HR, and respiratory rates) at the following times:
  - immediately before the pembrolizumab infusion
  - within 10 minutes following the conclusion of the pembrolizumab infusion
  - immediately before the tabelecleucel infusion
  - within 10 minutes following the conclusion of the tabelecleucel infusion
  - 1 hour (± 10 minutes) after initiation of the tabelecleucel infusion
  - **Cycle 1 only:** 2 hours (± 10 minutes) after initiation of the tabelecleucel infusion
  - If the subject experiences symptoms/signs of an infusion reaction, follow-up may be longer, as clinically indicated.

6.3.2 *Treatment/Consolidation: Day 8 and Day 15*

- Physical examination including weight
- Concomitant medications
- AEs
- CCI [redacted]
- **Cohort 1, checkpoint inhibitor (PD-1/PD-L1) failed subjects only, at least 1 day after Cycle 1 Day 8 and prior to Cycle 1 Day 15:** tumor/active site biopsy as described in Section 7.2 (central laboratory); hematology and coagulation panels must be performed prior to biopsy
- **Cohort 1, Day 15 only,** Hematology panel: CBC with platelet count and differential

- **Cohort 1, Day 15 only,** Full chemistry panel: sodium, potassium, chloride, total carbon dioxide, BUN, creatinine, glucose (fasting), total calcium, albumin, total protein, serum creatinine, TBILI, ALT, AST, alkaline phosphatase, and tests of thyroid function (TSH, T3, and T4)
- **Cohort 2, at least 1 day after Cycle 1 Day 8 and prior to Cycle 1 Day 15 optional** tumor/active site biopsy as described in Section 7.2 (central laboratory); hematology and coagulation panels must be performed prior to biopsy
- **Cycle 1 and Cycle 2 Day 15 only:** CCI [redacted]
- Investigational product infusion: tabelecleucel
- Vital signs (body temperature, BP, HR, and respiratory rates) at the following times:
  - immediately before the infusion
  - within 10 minutes following the conclusion of the infusion
  - 1 hour (± 10 minutes) after initiation of the infusion
  - If the subject experiences symptoms/signs of an infusion reaction, follow-up may be longer, as clinically indicated.

6.3.3 Treatment/Consolidation, Observation: Days 16 to 21

Between Days 16 to 21 of each cycle, the following *required* assessments/procedures will be performed:

- Concomitant medications
- AEs
- **Cycle 2 and subsequent cycles:** Radiographic assessments (MRI or CT with contrast) as described in Section 7.1

6.4 Maintenance Phase (84-day Cycles)

The Maintenance Phase will start 21 days after Day 1 of the previous treatment cycle. During the Maintenance Phase, subjects will receive tabelecleucel on Day 1 and pembrolizumab on Day 1, Day 21 (± 2), Day 42 (± 2), and Day 63 (± 2) followed by a response assessment at the observation visit on Day 77 (± 2) of each 84-day cycle until disease progression, unacceptable toxicity, or a total of 35 infusions of pembrolizumab (including for treatment, consolidation, and/or maintenance) have been given.

6.4.1 Maintenance: Day 1

- Physical examination including weight
- AEs
- Concomitant medications

- Hematology panel: CBC with platelet count and differential
- Full chemistry panel: sodium, potassium, chloride, total carbon dioxide, BUN, creatinine, glucose (fasting), total calcium, albumin, total protein, serum creatinine, TBILI, ALT, AST, alkaline phosphatase, and tests of thyroid function (TSH, T3, and T4)
- CCI [redacted]
- **Maintenance Cycle 1 only:** CCI [redacted]
- Investigational product infusions:
  - Pembrolizumab will be administered prior to tabelecleucel
  - Tabelecleucel will be administered 1 hour (± 10 minutes) after completion of the administration of pembrolizumab only if no infusion reactions related to pembrolizumab are observed/reported or in the case of such a reaction, the subject has recovered
- Vital signs (body temperature, BP, HR, and respiratory rates) at the following times:
  - immediately before the pembrolizumab infusion
  - within 10 minutes following the conclusion of the pembrolizumab infusion
  - immediately before the tabelecleucel infusion
  - within 10 minutes following the conclusion of the tabelecleucel infusion
  - 1 hour (± 10 minutes) after initiation of the tabelecleucel infusion
  - If the subject experiences symptoms/signs of an infusion reaction, follow-up may be longer, as clinically indicated.

6.4.2 Maintenance: Day 21, Day 42, and Day 63

- Physical examination including weight
- AEs
- Concomitant medications
- Hematology panel: CBC with platelet count and differential
- Abbreviated chemistry panel: serum creatinine, TBILI, ALT, AST, alkaline phosphatase, glucose (fasting) and tests of thyroid function (TSH, T3, and T4)
- **Maintenance Cycle 1 Day 21 only:** CCI [redacted]
- Investigational product infusion: pembrolizumab

- Vital signs (body temperature, BP, HR, and respiratory rates) at the following times:
  - immediately before the infusion
  - within 10 minutes following the conclusion of the infusion
  - 1 hour (± 10 minutes) after initiation of the infusion
  - If the subject experiences symptoms/signs of an infusion reaction, follow-up may be longer, as clinically indicated.

6.4.3 Maintenance: Day 77

- Radiographic assessments (including CT with contrast or MRI) as described in Section 7.1
- Concomitant medications
- AEs

6.5 End-of-Treatment Visit

An End-of-Treatment visit will be performed 30 ± 5 days after the last dose of investigational product (tabelecleucel and/or pembrolizumab) for all subjects, including those who discontinue early from treatment, consolidation, and/or maintenance. The following assessments/procedures will be performed:

- Physical examination including weight
- Concomitant medications
- AEs
- Vital signs (body temperature, BP, HR, and respiratory rate)
- Hematology: CBC with platelet count and differential
- Full chemistry panel: sodium, potassium, chloride, total carbon dioxide, BUN, creatinine, glucose (fasting), total calcium, albumin, total protein, serum creatinine, TBILI, ALT, AST, alkaline phosphatase, and tests of thyroid function (TSH, T3, and T4)
- CMV antibody (if negative at baseline)
- Pregnancy test for women of childbearing potential (serum)
- Performance status: ECOG for subjects > 16 years of age or Lansky score for subjects 12 to 16 years of age
- CCI [redacted]
- CCI [redacted]
- **Only if within 30 days from the last dose of tabelecleucel:** CCI [redacted]

- Radiographic assessments (including CT with contrast or MRI) as described in Section 7.1

6.6 Quarterly Follow-up

Quarterly Follow-up will occur every 90 ± 14 days for 12 months after the last dose of investigational product (tabelecleucel and/or pembrolizumab) or until disease progression. The last Quarterly Follow-up Visit will be considered the end-of-study for the subject. The following assessments/procedures will be performed:

- Radiographic assessments including CT with contrast or MRI for subjects with CR, PR, or SD who did not complete maintenance cycles until 35 infusions of pembrolizumab was given or until disease progression - as described in Section 7.1
- Survival and disease status (ie, an investigator assessment based on clinical and radiographic assessments)
- For AEs reporting, refer to Section 8.5

6.7 Early Withdrawal

For subjects who discontinue early from treatment, consolidation, or maintenance, the reason for discontinuation should be provided and the End-of-Treatment visit should be performed. The subject will be entered into Quarterly Follow-up, unless consent is withdrawn, for 12 months after the last dose of investigational product (tabelecleucel and/or pembrolizumab).

For a subject who discontinues early from quarterly follow-up, the reason for discontinuation should be provided and the last Quarterly Follow-up Visit will be considered the end-of-study for the subject.

7 EFFICACY AND SAFETY ASSESSMENTS

7.1 Radiographic Tumor Assessments

Local site study team reading (investigator assessment with site radiology reading) based on RECIST 1.1 and immune (i)RECIST will be used to determine subject eligibility and clinical treatment decisions during the course of the study. RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab to immune iRECIST. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the adaptations described in Section 15.5.

Disease progression will be based on radiographic measurements according RECIST 1.1 and iRECIST. For clinically stable subjects, if imaging shows progressive disease (unconfirmed

progressive disease), it is at the discretion of the investigator to keep a subject on treatment with investigational product or to stop treatment with investigational product until repeat imaging is performed 4-6 weeks later in order to confirm progressive disease since T-cell infiltration of a tumor can cause the appearance of radiographic progression in subjects who subsequently respond [49]. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation prior to stopping treatment. This decision will be based on clinical judgment of a subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data, and in consultation with the sponsor's medical monitor.

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.

7.1.1 Rationale for Endpoints Related to RECIST

The central radiology vendor will perform retrospective IRR of scans in support of primary and secondary study objectives. OS will be included as it is a standard assessment of clinical benefit in subjects with NPC. ORR and the duration of response by RECIST 1.1 criteria as assessed by IRR will serve as additional measures of efficacy.

RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Since the treatment assignment is unblinded, images read by a central imaging vendor blinded to treatment assignment (ie, IRR) can minimize bias in the response assessments. In addition, final determination of radiologic progression will be based on the central imaging vendor assessment of progression, rather than site study team assessment.

7.1.2 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor for IRR can be found in the Radiology Manual. Tumor imaging may be acquired by CT or MRI. For the abdomen and pelvis, contrast-enhanced 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 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 investigator at the study site and/or the radiological reviewer located at the site or at an offsite facility.

Imaging should include the chest, abdomen, pelvis, as well as the head and neck. Brain imaging is required for all subjects at screening. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Expedited confirmation of measurable disease based on RECIST 1.1 by IRR at screening will be used to determine subject eligibility. Confirmation by the central imaging vendor that the subject's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required prior to subject treatment.

All scheduled images for all study subjects from the study sites will be submitted to the central imaging vendor for IRR. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor for IRR.

7.1.2.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed prior to the date of the first dose of investigational product. The study site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted to the IRR vendor for retrospective confirmation of measurable disease per RECIST 1.1 for eligibility prior to the date of the first dose of investigational product. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and can be assessed by the central imaging vendor.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

7.1.2.2 Tumor Imaging During the Study

The first on study imaging assessment should be performed after Treatment Cycle 2 Day 15 between Days 16 to 21, and thereafter, after each treatment and consolidation cycle Day 15 between Days 16 to 21. Subsequent tumor imaging should be performed during the Maintenance Phase on Day 77 (± 2 days) of each cycle, at the end-of-treatment (30 ± 5 days after the last dose of investigational product), and during the Quarterly follow-up phase (every 90 ± 14 days), or more frequently if clinically indicated.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm an initial treatment response of PR or CR will occur during the subsequent consolidation cycle.

Per iRECIST (Section 7.1.4), disease progression should be confirmed by the study site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease 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 Section 7.1.4. 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 study site, will discontinue treatment with investigational products. Exceptions are detailed in Section 7.1.4.

7.1.2.3 End-of-Treatment and Quarterly Follow-up Tumor Imaging

For subjects who discontinue treatment with investigational products, tumor imaging should be performed at the End-of-Treatment Visit (30 ± 5 days after the last dose of investigational

product). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For subjects who discontinue both investigational products due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.3 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by IRR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Imaging will be repeated during subsequent treatment/consolidation cycles (between Days 16 to 21), maintenance cycles on Day 77 of each cycle, End-of-Treatment (30 ± 5 days after the last dose of investigational product), and Quarterly Follow-up every 90 (± 14) days for 12 months after the last dose of investigational product or until disease progression. Refer to the study Schedule of Assessments (Section 15.1), as well as in the Procedures: Section 6.3, Section 6.4.3, Section 6.5, and Section 6.6, respectively.

7.1.4 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. A description of the adaptations and iRECIST process is provided in Section 15.5 with additional details in the iRECIST publication [40]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 7 and illustrated as a flowchart in Figure 2.

iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, subjects should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Section 15.5, and in consultation with the sponsor's medical monitor. This allowance to continue treatment despite initial radiologic progressive disease takes into account the observation 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.

Table 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of progressive disease by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm progressive disease.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST, see Figure 1[a]	Repeat imaging at 4 to 8 weeks to confirm progressive disease per investigator's discretion only.	Discontinue pembrolizumab. May be allowed to be treated with a tabelecleucel product with a different HLA restriction (if available) in consultation with the sponsor's medical monitor, see Figure 1.
Repeat tumor imaging confirms progressive disease (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue pembrolizumab (exception is possible upon consultation with Sponsor). May be allowed to be treated with a tabelecleucel product with a different HLA restriction in consultation with the sponsor's medical monitor, see Figure 1.	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm progressive disease. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion, see Figure 1[a]	Repeat imaging at 4 to 8 weeks to confirm progressive disease per investigator's discretion only.	Discontinue pembrolizumab. May be allowed to be treated with a tabelecleucel product with a different HLA restriction (if available) in consultation with the sponsor's medical monitor, see Figure 1
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. Refer to Figure 1 for details.	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. Refer to Figure 1 for details.

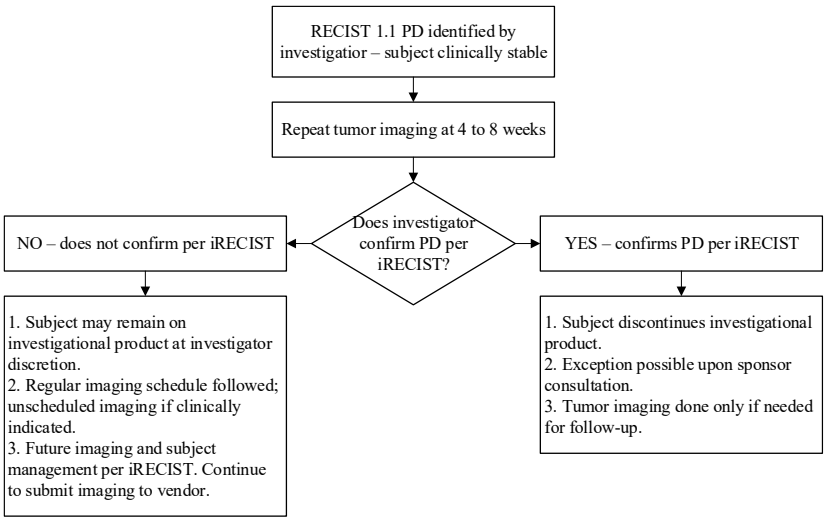
Table 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**

Abbreviations: IRR: Independent Radiographic Review; 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; RECIST 1.1: Response Evaluation Criteria in Solid Tumors 1.1.

[a] For a clinically stable subject with first radiographic evidence of progressive disease by RECIST 1.1 (ie, unconfirmed progressive disease), it is at the discretion of the investigator not continue treating the subject with the assigned treatment per protocol until cPD at least 28 days from the date of the scan first suggesting progressive disease. If radiographic progression is not confirmed by iRECIST per the investigator, then the subject may continue on treatment and follow the regular imaging schedule intervals until cPD at a later point by the study site in consultation with the medical monitor.

Figure 2 Imaging and Treatment for Clinically Stable Subjects Treated with Tabelecleucel and Pembrolizumab after First Radiologic Evidence of Progressive Disease Assessed by the Investigator



7.2 Laboratory Assessments

7.2.1 Local Laboratory Tests

Routine safety laboratory tests will be performed by local laboratories and results from these tests will be reported.

A serum pregnancy test will be performed.

CMV antibody will be collected at the study sites and analysis will be performed by the local laboratory.

The hematology panel will comprise the following parameters: CBC (red blood cells, hematocrit, hemoglobin, white blood cells) with differential (absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and platelets.

The coagulation panel will comprise the following parameters: PT, aPTT, and INR.

The full chemistry panel will comprise the following standard parameters: sodium, potassium, chloride, total carbon dioxide, BUN, creatinine, glucose (fasting), total calcium, albumin, total protein, serum creatinine, TBILI, ALT, AST, alkaline phosphatase, and tests of thyroid function (TSH, T3, and T4).

The abbreviated chemistry panel will consist of serum creatinine, TBILI, ALT, AST, alkaline phosphatase, glucose (fasting) and tests of thyroid function (TSH, T3, and T4).

High resolution HLA typing is comprised of DNA-level data for HLA-A, -B, -C, -DRB1, and -DQB1. Historical high-resolution HLA typing data are acceptable; but if these data are not available, high resolution typing will be performed so that HLA matching can be determined prior to enrollment.

7.2.2 Central Laboratory Tests

A tumor/active site core needle, incisional or excisional biopsy is required; fine needle aspirate is not for the purposes of this biopsy; hematology and coagulation panels must be performed prior to biopsy. Subjects for whom a new biopsy cannot be obtained (eg, inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the sponsor. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Samples will be collected and shipped to a central laboratory according to the instructions in the Laboratory Manual.

7.2.3 Reporting Routine Laboratory Abnormalities

Laboratory test results along with appropriate normal ranges are to be reported routinely in the appropriate electronic data capture form. In addition, the investigator is responsible for reviewing laboratory test results and determining whether they meet AE reporting criteria (see Section 8), in which case they are to be reported on the adverse event form as well.

8 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory value), symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product [19].

Out of range laboratory values that are assessed as clinically meaningful per investigator's medical judgement must be reported as AEs with severity grading (see Section 8.3), even if they are asymptomatic. The investigator is responsible for reviewing all laboratory test results (either collected as per protocol or for any other reason) and determining whether an abnormal value in an individual subject is clinically meaningful. When part of a clinical condition, the underlying diagnosis should be listed as the AE in preference to the abnormal laboratory value (eg, anemia rather than low hemoglobin). If a unifying diagnosis is not available, then the sign(s)/symptom(s) must be reported as AE(s) in addition to the laboratory abnormality.

A laboratory value that is determined to be erroneous does not require reporting as an AE; however, any AE resulting from an action taken to treat a subject with an erroneous laboratory value should be reported as such (eg, an adverse reaction or worsening medical condition resulting from any clinical intervention based on the laboratory result).

Investigators must report all AE terms (ie, diseases/diagnoses, symptoms, or signs) and determine their seriousness criteria (Section 8.1) and severity grade (Section 8.3), as well as assess their relationship to the investigational product (Section 8.4).

If an AE changes seriousness criteria or severity grade, that event will be ended and a new AE with the changed seriousness criteria or severity grade will be recorded. Changes to other AE attributes (eg, causality) should be evaluated by the investigator to determine if a new event should be recorded.

Treatment-emergent AEs (TEAEs) are defined as events not present prior to the initiation of study product or any event already present that worsens in either intensity of frequency following exposure to study treatment.

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, dental extraction, transfusion); the condition that necessitates the procedure is the AE

- Any pre-existing disease or condition or laboratory abnormality which is present prior to the start of the study product and that does not worsen
- Situations where an adverse medical event has not occurred (ie, hospitalization for elective surgery, social admission)

8.1 Serious Adverse Events

An SAE is defined as an AE that in the view of either the investigator or the sponsor:

- Results in death
- Is life-threatening, defined as an event in which the subject was, in the judgment of the investigator, at immediate risk of death. This does not include an AE that, had it occurred in a more serious form, might have caused death.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

In addition, important medical experiences that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

NOTE: In addition to the above criteria, AEs meeting any of the following criteria, although not SAEs per ICH definition, are reportable to the sponsor in the same timeframe as SAEs to meet certain local requirements:

- New cancer (that is not a condition of the study)
- AE associated with an overdose
- AEs of special interest (refer to Section 8.2)

All subjects with SAEs must be followed up until no further resolution is expected.

8.1.1 Serious versus Severe Adverse Events

To avoid confusion between the terms “serious” and “severe” which have different implications in the context of a clinical study, the following definitions are provided [19]:

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild/ grade 1, moderate/grade 2, severe/grade 3, life-threatening/grade 4, and death/grade 5). However, the event itself may be of only minor medical significance (eg, a severe headache). This is not the same as “serious”, which is based on a subject/event outcome or action criteria

associated with events that threaten a subject's life or function. Seriousness (not severity) serves as a guide to the sponsor to determine regulatory reporting obligations.

8.1.2 Serious Adverse Event Definition Clarifications

Death is a result of an SAE, and not an SAE itself. The event that, in the investigator's judgment, caused the death is the SAE.

Life-threatening means that the subject was at immediate risk of death from the event as it occurred. Life-threatening does not include an event that might have led to death, had it occurred with greater severity.

In-patient hospitalization means the subjects has been formally admitted to a hospital for a medical cause, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is considered an SAE).

The principal investigator should attempt to establish a diagnosis of an event based on signs, symptoms, and test results or other medical information (when obtained). In such cases, the diagnosis should be documented as the AE rather than the individual signs or symptoms.

8.2 Adverse Events of Special Interest

An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. All AEs of special interest must be reported in a manner similar to SAEs (see Section 8.5.1).

8.2.1 Adverse Events of Special Interest for Pembrolizumab

AEs of special interest for pembrolizumab for this study include:

1. An overdose of sponsor's product, as defined in Section 8.2.3, that is not associated with clinical symptoms or abnormal laboratory results
2. An elevated AST or ALT value that is ≥ 3 x ULN and an elevated TBILI value that is ≥ 2 x ULN and, at the same time, an alkaline phosphatase value that < 2 x ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing

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

and the sponsor's medical monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not AEs of special interest for this study.

8.2.2 Adverse Events of Special Interest and Possible Risks for Tabelecleucel

Tabelecleucel consists of partially HLA-matched, human-derived products using healthy donor PBMCs as starting material. Because of these features, several AEs of special interest (noted in italics in this section) will be monitored in this study. *Infusion reactions* and *transmission of infectious disease* can occur with any human-derived product and therefore, such events are considered of special interest. Other T-cell products, specifically chimeric antigen receptor (CAR)-T cells, have been associated with *cytokine release syndrome (CRS)*; though this phenomenon has not been observed in studies with tabelecleucel cell products, this AE is also considered of special interest. Because tabelecleucel is generated from starting material consisting of donor material that includes donor T cells, *GvHD* is also an AE of special interest.

As with any investigational product, there are potential risks associated with tabelecleucel; these risks are listed below for convenience. However, please refer to the current edition of tabelecleucel (ATA129) Investigator's Brochure for further details, including risk mitigation, as well as for up to date risk information.

- Tumor flare reaction
- GvHD
- CRS
- Marrow or organ rejection
- Transmission of CMV infection
- Transmission of other infections
- Infusion-related reactions

8.2.3 Treatment of Overdose

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

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

8.3 Severity (or Grading) of Adverse Events

The severity of each AE will be determined using a severity grading system, which could be either the CTCAE or the categorical descriptions (mild, moderate, severe, life-threatening, or death); refer to CTCAE version 5 [47] If the event is listed in the CTCAE tables, the grading scale with clinical descriptions will be used to determine the grade of the event. If the event is not listed in the CTCAE tables, the categorical descriptions will be used, and clinical judgement should be applied to map the severity of the event to the CTCAE grade.

NOTE: the CTCAE system should not be used as a restrictive selection of event terms; ie, the diagnosis term should never be altered to accommodate the CTCAE grade. If the exact term is not listed in the CTCAE, the severity of the event may be based on the closest/similar medical concept from the CTCAE or based on the severity alternative options and mapped to the appropriate CTCAE grade.

For the following AEs, which are not described in the CTCAE, refer to the indicated information for a recommended severity grading system.

- Acute GvHD: refer to Section 15.6.1
- Chronic GvHD: refer to Section 15.6.2

8.4 Relationship of Adverse Events to Investigational Product

The investigator must assess and report all AEs and evaluate for their relationship to the study product (tabelecleucel or pembrolizumab) according to the following definitions:

Unrelated: The AE is definitely not associated with administration of investigational product and is judged related to causes other than the investigational product. This category also applies when there is considerable likelihood of a cause other than the investigational product.

Possibly Related: A causal relationship between treatment with the investigational product and the AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. This implies a lesser degree of certainty about causality than a related AE. Additional evidence to suggest a suspected adverse reaction includes:

- Occurrence of uncommon AEs that are known to be strongly associated with investigation product exposure (eg, anaphylaxis, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, Stevens-Johnson Syndrome)
- Occurrence of AEs that are uncommon in the study population, but not commonly associated with investigational product exposure (eg, intussusception in healthy infants)

Related: A causal relationship between the investigational product administration and the AE is definite or very likely.

These criteria, in addition to the principal investigator's clinical judgment, should be used as a guide for determining the causal assessment. If the event is considered unrelated to

investigational product administration, then an alternative explanation should be provided, as applicable.

8.5 Adverse Event Reporting Requirements

AEs, including SAEs will be reported by the subject (or, when appropriate, by the subject's legally authorized representative) to the investigator. 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 in the electronic case report form (eCRF). Investigators remain responsible for following up AEs for outcome.

AE reporting requirements are as follows:

- AEs assessed by the investigator as at least possibly related to study procedure(s) occurring from the date that the first informed consent is signed to before the first dose of investigational product
- All AEs, related and unrelated, occurring from the first administration of any investigational product through 30 days after the last investigational product
- AEs assessed by the investigator as at least possibly related to any investigational product or study procedure(s) occurring after 30 days from the last investigational product exposure

In addition, for the indicated events, refer to the following sections:

- Deaths, see Section 8.5.1
- SAEs, including AEs of special interest, see Section 8.5.1
- Pregnancies and exposures during lactation, see Section 8.5.2
- Laboratory abnormalities as an AEs, see Section 8

Disease progression without secondary complications should be reported as an AE of disease progression (eg, a new metastasis or tumor increase) and not the indication for which subject entered the study (ie, EBV^+ NPC). If the event is a complication of disease progression, the complication should be reported along with the event of disease progression (eg, a recent increase in bronchial tumor leading to pneumonia should be reported as “disease progression” and “pneumonia”).

8.5.1 Serious Adverse Event Reporting Requirements

The sponsor must be notified immediately regarding information on any life-threatening or fatal SAE that is attributed to the investigational product by the investigator. This is to be followed by submission of written case details in eCRF and on the required paper reporting forms within 24 hours of the study site’s knowledge of the event and as described in the eCRF completion guide and the safety reporting instructions in the study manual.

All SAEs, including AEs of special interest, occurring from the first dose of investigational product through 90 days following the last dose of investigational product, or through 30 days

following cessation of investigational product if the subject initiates a new non-protocol therapy for EBV^+ NPC, whichever is shorter, must be reported to sponsor within 24 hours of the study site's knowledge of the event.

All deaths occurring within 30 days after the last dose of investigational product must be reported to the sponsor within 24 hours of the study site's knowledge of the event.

The core information when reporting an SAE is as follows:

- Subject's study identification number, principal investigator's name, and site number
- SAE information: event term, onset date, severity and causal relationship to the study product
- Seriousness Criteria: eg, death, life-threatening, in-patient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event
- A summary of relevant medical history, pertinent laboratory data or other test results
- The first and last dates of investigational product administration, and indication whether the investigational product was discontinued or the schedule of administration was modified
- NOTE: Care should be taken to redact any identification information (name, address, etc.) from any records being sent in to the sponsor/designee for safety review to protect subject confidentiality

In the event of an SAE, the report should be sent within 24 hours with as much information as is available at the time (including discharge summaries, autopsy reports, death certificates, or any other pertinent documentation). Supplemental information may be provided using a follow-up report and should not delay the initial report. The sponsor, or designee, may contact the investigational site to solicit additional information or to follow-up on the event.

Collect and maintain in the medical record all pertinent information and medical judgments from colleagues who assisted in the treatment and follow-up of the subject, including hospital discharge summaries, progress notes, admission or emergency room notes, and discharge summaries. The investigator should supply the sponsor and the Independent Ethics Committee (IRB)/ Independent Ethics Committee (IEC) with any additional requested information (eg, resolution information, autopsy reports, death certificates).

8.5.2 Pregnancy Reporting Requirements

All pregnancies or lactations in a female subject or the female partner of a male subject occurring after the informed consent form is signed and through 120 days following the last dose of investigational product, or through 30 days following cessation of investigational product if the subject initiates a new non-protocol therapy for NPC is initiated, whichever is shorter must be reported to the sponsor within 24 hours of the study site's knowledge of the event per the study

guidance documents. Neither pregnancy, lactation, nor an induced elective abortion to terminate a pregnancy for non-medical reasons is considered an AE.

A female subject who inadvertently becomes pregnant during treatment with investigational product will be immediately discontinued from treatment. A male subject who causes his partner to become pregnant will not need to discontinue from treatment. The investigator should counsel the subject/subject's female partner regarding the unknown risks of tabelecleucel and pembrolizumab on the fetus and the need to inform the investigator of the outcome of the pregnancy. The subject/subject's female partner must also be encouraged to schedule regular prenatal visits with an appropriately qualified health care provider and should inform the investigator of any problems with the pregnancy. The investigator will contact the female subject (or female partner of a male subject, if consent is given) at least monthly and document the subject's (or female partner'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 an SAE (ie, important medical event) including: death (fetal death, neonatal death [including all neonatal deaths that occur within 1 month of the expected birth date ie, either before or after the expected birth date], infant death occurring 1 month after birth, if the investigator assesses the death as possibly related to in utero exposure to study treatment, miscarriage and stillbirth), abortion (spontaneous abortion, induced therapeutic abortion to terminate a pregnancy due to complications or other medical reasons, or missed abortion), congenital anomaly (live birth or aborted fetus), or other disabling or life-threatening complication to the mother or newborn (eg, blighted ovum, benign hydatidiform mole). The 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. If the end of pregnancy occurs after the study has been completed, the outcome should be reported directly to the sponsor.

8.5.3 Investigator Reporting to the Institutional Review Board/Independent Ethics Committee

AEs/SAEs are to be reported to the local IRB/IEC, according to the policy of the local committee/board. If reporting is required, a copy of the IRB/IEC notification must be maintained at the site.

8.5.4 Sponsor Reporting Requirements

The sponsor or its designee is responsible for submitting expedited safety reports to the regulatory agency(s) for all confirmed serious unexpected suspected adverse reactions (SUSARs). These reports will comply with local and regional requirements and with the ICH Guideline [19]. The sponsor or designee will notify the appropriate regulatory authority within 7 days (for fatal or life-threatening SUSARs) after the sponsor's initial receipt of the information or 15 days (for all other SUSARs) after the sponsor determines that the information qualifies for reporting. The sponsor or designee will notify the investigators and IRBs, unless the investigator is responsible for informing the IRB directly. The sponsor (or designee) will follow safety reporting guidelines according to regional and local requirements.

9 STATISTICS

9.1 Analysis Populations

The efficacy and safety populations will include all subjects enrolled in the study and who receive any investigational product. The efficacy population will be for the primary efficacy analyses, and all analyses of disposition, demographic and baseline disease characteristics.

In order for a subject to be considered evaluable for the analysis of DLT, the subject should have either had a DLT during the 21-day DLT assessment window or had completed the 21-day DLT assessment. Otherwise, a replacement subject will be added to Cohort 1.

9.2 Efficacy Analysis

For estimation purposes, the primary endpoint (ie, ORR) will be analyzed using the exact one-sample binomial test at the 1-sided alpha = 0.025 significance level. A one-sided 2.5% exact test will be used. The null hypothesis is ORR ≤ 20% and the targeted ORR is ≥ 45%. The point estimate of ORR and the corresponding 95% CI will be provided. Cohort 1 subjects who are PD-1 or PD-L1 naïve treated at the RP2D will be included in the primary efficacy analysis.

The distributions of DOR, PFS, OS, and other time-to-event endpoints will be summarized using the Kaplan-Meier method. Efficacy endpoints that are defined as proportions, including CR rate and iRR, will be summarized using two-sided exact binomial 95% confidence intervals (CIs).

The primary analysis of the tumor response-based endpoints will be based on tumor assessments following administration of up to 2 tabelecleucel cell products.

9.3 Safety Analysis

AEs will be mapped using the Medical Dictionary for Regulatory Activities (MedDRA), version 18, to system organ classes (SOCs) and preferred terms (PTs).

AEs will be graded according to CTCAE version 5, except for certain events (see Section 8.3), as determined by the investigator.

9.4 CCI [redacted]

CCI [redacted]

CCI [redacted]

9.5 Sample Size Determination

The estimated ORR for treatment with the combination of tabelecleucel and pembrolizumab is ≥ 45%. The comparator ORR deemed uninteresting is 20%. Based on the exact binomial test at the 1-sided alpha = 0.025 significance level, a sample size of 36 subjects will provide 90% power to detect a true ORR of at least 45%.

10 DATA COLLECTION, RETENTION, AND MONITORING

10.1 Data Collection and Retention

10.1.1 Data Collection Instruments

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the investigational product.

Designated study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the sponsor (or designee), but will be identified by a site number, subject number.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The investigator is responsible for reviewing and signing all information collected on subjects enrolled this study for completeness and accuracy. A copy of the eCRF will remain at the investigator's site at the completion of the study.

10.1.2 Data Management Procedures

The data will be entered into a validated database. The sponsor-designated data management group will be responsible for data processing, in accordance with sponsor's and/or designee's standard operating procedures for clinical studies. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH Good Clinical Practice (GCP) and applicable regional or national regulations for the handling and analysis of data for clinical studies.

10.1.3 Electronic Case Report Forms

The eCRF will be provided by the sponsor or its representatives and should be completed in accordance with applicable guidelines. Each eCRF should be filled out completely by the investigator or designee as stated in the Delegation of Authority Log. All data entry in the eCRF should have corresponding source documentation filed in the subject study records.

All data will be stored in a validated database that is compliant with ICH GCP and regional or national regulations. The principal investigator is responsible for ensuring the timely completion and submission of the eCRFs. The principal investigator must review, electronically sign and date the eCRFs at the time of study completion.

10.1.4 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked and resolved through the electronic data capture system directly. Queries shall be replied to and when applicable updates to data will be done in the study database. All changes to the study database will be documented in the system's audit trail.

10.1.5 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (eg, production of interim and final reports), data for analysis will be locked and cleaned per established procedures, if applicable.

10.1.6 Source Document Maintenance

Source documents are defined as documentation of the observations and activities of a clinical study. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, subject quality of life surveys, subject diaries (if applicable), computer printouts, laboratory data, and recorded data from automated instruments. All source documents for this study will be maintained by the investigator in accordance with ICH GCP and applicable regional or national regulations and made available to the sponsor/sponsor's representative or regulatory authority. The official signed informed consent form (ICF) for each subject will be maintained as a source document, and a copy provided to the subject or their legal representative.

When paper source documents are used, ICH GCP and applicable regional or national regulations document guidelines should be followed. For example, incorrect entries should be crossed out with a single pen stroke. Corrections must be made adjacent to the item to be altered, initialed and dated with the reason for the correction if necessary by the investigator or designee. Overwriting of data or use of liquid correction fluid is not allowed.

10.1.7 Investigational Product Accountability

At all times, a record of the investigational product inventory and investigational product accountability must be maintained. Inventory and accountability records must be readily available to the study monitor, the sponsor, and any regulatory authority. The investigator, in conjunction with the site infusion lab/pharmacist, is responsible for ensuring accountability of all used and unused investigational product.

All received, dispensed, and returned investigational product supplies are to be reconciled on an ongoing basis and will be recorded on the Investigational Product Accountability Log. Following investigational product accountability verification by the study monitor, the study site may return all used investigational product supplies to the sponsor or designee (tabelecleucel only). Following investigational product accountability verification by the study monitor, the site may return all unused investigational product supplies to the sponsor or designee. During the conduct of the study, it is preferable that used cryovials be returned to the sponsor or designee; however, used cryovials may be destroyed on-site if required per institutional policy, and destruction is performed ensuring compliance with ICH GCP and applicable regional or national regulations.

10.2 Study Monitoring and Administrative Considerations

10.2.1 Study Monitoring

The monitor, as a representative of the sponsor and/or designee, has the obligation to follow the study closely. As such, the monitor may visit the investigative site at periodic intervals, and maintain necessary contact through telephone, e-mail, and letter. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion on the conduct of the study with the investigator and study staff.

The monitor, as authorized by the sponsor, will be given direct access to all study related documentation (such as medical charts/records, laboratory reports, diagnostic reports, etc.).

10.2.2 Documentation of Protocol Deviations

A protocol deviation is a departure from the procedures and/or processes described in the protocol as prepared by the sponsor, agreed to by the investigator or sub-investigator, and approved by the IRB/IEC.

Protocol deviations should be reported to the sponsor or designee as they occur or are discovered and should be documented as appropriate in the source record. In addition, protocol deviations should be reported to the IRB/IEC per IRB/IEC guidelines. The monitor will document deviations discovered throughout the course of monitoring visits, or medical review of the clinical database. These deviations and corrective actions, when appropriate, will be reviewed and discussed with the sponsor and the investigators as applicable.

Study monitoring will be performed in accordance with ICH GCP, the sponsor's and/or the designee's procedures, the protocol, and applicable local regulations.

10.2.3 Study Completion

Atara Biotherapeutics, Inc. requires the availability of the following data and materials before the site close out visit can take place including the following:

- Laboratory findings, clinical data, and all study test results from inventory check through the last study visit

- eCRFs (including queries) properly completed by appropriate study staff and electronically signed and dated by the investigator
- Complete drug accountability records for all drug shipped to the site (drug inventory log and an inventory of returned or destroyed investigational product)
- Copies of all IRB/IEC documentation including approvals of the original protocol, amendments (if applicable), informed consent documents and other notifications, if appropriate
- A summary of the study prepared by the investigator (ie, the IRB/IEC summary letter)
- A Financial Disclosure Form will be collected at the close-out visit, and up to 1 year following completion of the study

After the study site close-out visit is completed, IRB/IEC acknowledgment of study closure must be provided to Atara Biotherapeutics, Inc. or its representative.

10.2.4 Audits and Inspections

During and/or after completion of the study, quality assurance auditors acting on behalf of sponsor or a regulatory authority may wish to perform on-site audits/inspections (ICH GCPs). The purpose of an audit, which is independent from routine monitoring, is to evaluate study conduct and compliance with the protocol, procedures, ICH GCP, and applicable regional or national regulations.

The investigators accept that by endorsing the protocol signature page that the sponsor, IRB/IEC or regulatory authorities may conduct an inspection to verify compliance of the study with ICH GCP. Representatives of the sponsor, IRB/IEC or regulatory authority may be permitted direct access to source documents. If a regulatory authority, or IRB/IEC notifies the investigator of an inspection, the investigator agrees to immediately notify the sponsor and provide the reason, if any, for the audit/inspection. The investigator agrees to promptly provide the sponsor with copies of any feedback (eg, Food and Drug Administration form 483, audit reports) issued at the end of the audit/inspection.

10.2.5 Confidentiality

Data collected during this study may be used to support the development, registration or marketing of investigational product or for related publications. Investigators, members of the study team, monitors, auditors, and regulators should handle all study specimens, evaluation forms, reports, and other records in a manner that protects the privacy and confidentiality of study subjects. These individuals should all be fully informed of relevant national/local laws/regulations related to privacy and confidentiality.

To protect subject confidentiality, only the sponsor's subject identification code and age should be recorded on any form or biological sample submitted to the sponsor or its designee's, IRB/IEC or laboratories. Investigators must establish secure safeguards to maintain the privacy of any screening logs that associate the sponsor's subject identification code to subject names and addresses.

All required written authorization, including the ICF is to be obtained from each subject and/or their legal representative prior to enrollment into the study in accordance with the applicable requirements (eg, the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information), and all applicable updates (eg, 2013 Omnibus Rule), and any other applicable regional or national requirements.

The investigator and/or relevant site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2.6 Financing and Insurance

The financing and insurance for this study are outlined in the clinical study agreement.

10.2.7 Study Termination Criteria

The sponsor has every intention of completing the study. However, the sponsor reserves the right to terminate a study site or this clinical study at any time. Reasons for termination may include, but are not limited to:

- Unacceptable safety and tolerability of tabelecleucel or pembrolizumab
- Serious or persistent noncompliance by the investigator with the protocol, clinical research agreement, ICH GCP, and applicable regional or national regulations in conducting the study
- IRB/IEC decision to terminate or suspend approval for the investigator
- Subject enrollment is unsatisfactory

11 ETHICS

11.1 Ethical Conduct of the Study

The investigator agrees that the study will be conducted according to the principles of the ICH GCP. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

11.2 Ethics Review by the Institutional Review Board or Independent Ethics Committee

ICH GCP and applicable regional or national regulations require that approval be obtained from an IRB/IEC prior to participation of human subjects in research studies. Prior to the study start, the protocol, Investigator's Brochure, ICF, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to the subject or subject's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals/acknowledgements, and of the IRB/IEC compliance with ICH GCP, will be

maintained by the site and made available for review and collection of copies by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC Chairman or designee and must identify the IRB/IEC by name and address, the clinical protocol by title and/or protocol number, amendment/version number and/or version date, and the date approval and/or favorable opinion was granted.

The investigator is responsible for performing the study in accordance with the IRB/IEC approved protocol/amendment(s). In the event of any deviation, the information will be reported to the sponsor and major deviations will be reported to the IRB/IEC as soon as possible or according to the local IRB/IEC guidelines.

Investigators will submit all written safety updates (provided by the sponsor) to the IRB/IEC, according to local IRB/IEC review requirements. The investigator is responsible for informing the IRB/IEC of the progress of the clinical study, reporting any non-administrative changes to the protocol, at intervals not exceeding 1 year or as otherwise specified by the IRB/IEC. The investigator and/or designee must supply the sponsor or its designee with written documentation of continued review of the clinical research. Investigators will provide a final report to the IRB/IEC when the study is complete, per IRB/IEC guidelines.

11.3 Informed Consent

Written informed consent in compliance with ICH GCP and applicable regional or national regulations and study site requirements will be obtained from each subject (or legally acceptable representative, as necessary) prior to the subject's entering the study or the performance of any study related procedures. An ICF template will be provided by the sponsor to study sites. Once study-specific modifications are proposed or made by the study site, the ICF must be reviewed and approved by the sponsor and/or its designee, prior to IRB/IEC submission. Once reviewed and all modifications agreed to by the sponsor and study site, the ICF will be submitted by the investigator and/or designee to his or her IRB/IEC for review and approval prior to the start of the study. If the ICF is revised during the course of the study, the subject and legally acceptable representative, if necessary, must sign the revised ICF if still participating in the study and as stipulated by the IRB/IEC. If applicable, the ICF will be provided in a certified translation of the subject's language.

Before any study procedures and enrollment, each prospective subject and legally acceptable representative, if necessary, will be given a full explanation of the study and provided sufficient time to read the IRB/IEC-approved ICF. Once the investigator or designee is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent for participation by signing and dating the ICF. The investigator or designee will also sign and date the ICF and document in the source documentation the time informed consent was obtained. The ICF must be signed by both the subject and investigator or designee prior to any study-related procedures.

If a potential subject is illiterate, visually impaired, and/or physically unable to provide a written signature, and does not have legally acceptable representative, the investigator must provide an

impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

In this study, assent will be obtained from the pediatric subject and consent from the subject's legally acceptable representative, except if the subject is very young, as defined by local law will apply. A pediatric subject is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical studies, under the applicable law of the jurisdiction in which the clinical study will take place. The IRB/IEC will determine the process for obtaining and documenting the assent process for pediatric subjects. The assent form will be in a language appropriate to the pediatric subject's age, experience, maturity and condition. A subject who reaches the age of maturity (ie, 18 years in most jurisdictions) during the course of the study will be provided the ICF for re-consent.

Once the signed and dated ICF (or assent form, as appropriate) has been obtained, a copy will be provided to the subject and legally acceptable representative, if necessary. The official signed and dated ICF and assent form will be placed in the subject's medical records at the study site, along with documentation of the informed consent process.

12 INVESTIGATOR'S RESPONSIBILITIES

12.1 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol and study guidance documents. In addition, the investigator agrees to submit annual reports to his/her IRB/IEC as appropriate.

12.2 Financial Disclosure and Obligations

According to ICH GCP and applicable regional or national regulations, the sponsor is required to completely and accurately disclose or certify information concerning the financial interests of the investigators. Investigators will also disclose if they are full- or part-time employees of regional or national authorities. Therefore, the investigator and relevant study staff (those that are listed as sub-investigators on the site Form 1572) must provide the sponsor and/or designee with sufficient, accurate financial certification of any financial arrangements that exist with the sponsor or in relation to the investigational product. In addition, the investigator and relevant study staff must provide to the sponsor and/or designee a commitment to promptly update this information if any relevant changes occur during the course of the study and for 1 year following the completion of the study.

12.3 Investigator Documentation

Prior to beginning the study, the investigator will provide the essential documentation in compliance with ICH GCP and applicable regional or national regulations.

12.4 Institutional Review Board

See Section 11.2.

12.5 Retention of Records

All essential study documentation (source documents, consent/assent forms, eCRFs, laboratory test results, and investigational product inventory records) at the study site should be retained in accordance with ICH GCP guidelines until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications or until at least 2 years following the formal discontinuation of development of the investigational product. Essential documents should be retained for a longer duration if required by a local regulatory authority or by agreement with Atara Biotherapeutics, Inc. The investigator must obtain written permission from Atara Biotherapeutics, Inc. before destroying essential documents.

The investigator/ study site will provide details of storage location for all study-related documentation to the sponsor or designee both during and after the study.

13 PUBLICATIONS

Atara Biotherapeutics, Inc. encourages publication of results obtained during the conduct of the clinical research that it sponsors. Publication includes presenting interim or final results in a peer-reviewed medical journal, or as an abstract and poster or oral presentation at a scientific meeting, or any other public presentation of clinical study results. Neither the institutions nor the investigators are permitted to publish the results of the study, in part, or entirely without the written authorization of the sponsor. The sponsor shall have the right to review and comment on any proposed publication prior to submission and may edit or remove any confidential information contained in the proposed publication. Additionally, the sponsor may delay the publication to establish and preserve its proprietary rights.

First Publication: The results of the entire multicenter study will be presented in a first publication after database lock, with authorship being determined by the sponsor and investigators using the criteria defined by the International Committee of Medical Journal Editors. At least 2 sponsor representatives will also be included as co-authors on the first publication of the results of the entire multicenter study to allow recognition of the sponsor's involvement in the design, clinical operations and management of the study.

Additional Publications: Subsequent publications of results of additional analyses must make reference to the first publication. Publications must include at least 2 sponsor staff to allow recognition of the sponsor's role. In all publications, the study must be identified by the study's identification number/code.

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15 APPENDIX

15.1 Schedule of Assessments and Procedures

Evaluation	Inventory Check[a]	Screening[a]	Treatment/Consolidation Cycles with Observation (21-day)[a]				Maintenance Cycles with Observation (84-day)[a]			EOT Visit[a]	Quarterly Follow-up[a]
			Day 1	Day 8	Day 15	Day 21	Day 1	Days 21, 42, 63	Day 77		
Signed informed consent	X	X									
High resolution HLA typing[b]	X										
Eligibility criteria		X									
CMV antibody status	X									X[c]	
Demographics	X										
Medical history		X									
Pregnancy test		X[d]								X[d]	
Physical examination		X	X	X	X		X	X		X	
Height and weight	X[e]	X	X[e]	X[e]	X[e]		X[e]	X[e]		X[e]	
Vital signs[f]		X	X[g]	X[h]	X[h]		X[g]	X[h]		X	
Performance status[i]		X								X	
Concomitant medications		X	X	X	X	X	X	X	X	X	
AEs[j]	X[k]	X[k]	X	X	X	X	X	X	X	X	X[l]
Hematology, coagulation and chemistry panels[m]		X[n]	X[o]		X[p]		X[p]	X[o]		X[p]	
CCI [redacted]											
CCI [redacted]											
CCI [redacted]											
Tumor/active site biopsy		X[t]		X[u]							

Evaluation	Inventory Check[a]	Screening[a]	Treatment/Consolidation Cycles with Observation (21-day)[a]				Maintenance Cycles with Observation (84-day)[a]			EOT Visit[a]	Quarterly Follow-up[a]
			Day 1	Day 8	Day 15	Day 21	Day 1	Days 21, 42, 63	Day 77		
Radiographic assessments[v]		X[w,x]				X[x]			X[x]	X[x]	X[w]
Tabelecleucel dosing[y]			X	X	X		X				
Pembrolizumab dosing[y]			X				X	X			
Survival and disease status											X

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, aPTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BP: blood pressure, BUN: blood urea nitrogen, CBC: complete blood count, CD: cluster of differentiation, CMV: cytomegalovirus, CR: complete response, CT: computed tomography, CCI , CCI , CCI , ECOG: Eastern Cooperative Oncology Group, EOT: End-of-Treatment, CCI HR: heart rate, HLA: human leukocyte antigen, ICF: informed consent form, INR: international normalized ratio, IV: intravenous(ly), MRI: magnetic resonance imaging, NPC: nasopharyngeal carcinoma, PD-1: programmed cell death protein-1, PD-L1: programmed death-ligand1, PR: partial response, PT: prothrombin time, SAE: serious adverse event, SD: stable disease, TBILI: total bilirubin, TSH: thyroid stimulating hormone.

a) PROCEDURAL NOTES:
Inventory check: within 5 to 10 days prior to screening
Screening: within 28 days prior to enrollment (Cycle 1 Day 1) or Days -28 to -1
Treatment and consolidation cycles (21-day): Day 1, Day 8 (± 2), Day 15 (± 2) and response assessment at the observation visit within 7 days after Day 15, except no response assessment after Treatment Cycle 1 Day 15
Observation: between Days 16 to 21 of each treatment/consolidation cycle
Maintenance cycles (84-day): Day 1, Day 21 (± 2), Day 42 (± 2), Day 63 (± 2), and Day 77 (± 2) until a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given
End-of-Treatment Visit: 30 ± 5 days after last dose (tabelecleucel and/or pembrolizumab) and for subjects who discontinue early
Quarterly Follow-up: every 90 ± 14 days after last dose (tabelecleucel and/or pembrolizumab) for 12 months or until disease progression. The last quarterly follow-up visit will be considered the end-of-study for the subject.

b) High resolution HLA typing includes HLA markers A, B, C, DRB1, and DQB1.

c) CMV antibody should be assessed at the end-of-treatment visit only if the subject was negative at baseline.

d) Pregnancy test within 72 hours prior to beginning Cycle 1 Day 1 and at EOT for women of childbearing potential only. Additional pregnancy testing may be conducted as per local regulations, where applicable.

e) Measure weight and height at screening only; for all other visits, measure weight only.

f) Vital signs include body temperature, BP, HR, and respiratory rate.

g) When 2 investigational products are administered on the same day, measure vital signs immediately before and within 10 minutes after the first (pembrolizumab) infusion, and immediately before, within 10 minutes, and at 1 hour (± 10 minutes) after the second (tabelecleucel) infusion. The second infusion (tabelecleucel) will only be administered if no infusion reactions related to pembrolizumab are observed/reported or in the case of such a reaction,

Evaluation	Inventory Check[a]	Screening[a]	Treatment/Consolidation Cycles with Observation (21-day)[a]				Maintenance Cycles with Observation (84-day)[a]			EOT Visit[a]	Quarterly Follow-up[a]
			Day 1	Day 8	Day 15	Day 21	Day 1	Days 21, 42, 63	Day 77		

the subject has recovered. For Cycle 1 Day 1 (the initial investigational product exposures), also measure vital signs 2 hours (± 10 minutes) after initiation of the second (tabelecleucel) infusion. If the subject experiences symptoms/signs of an infusion reaction, follow-up may be longer, as clinically indicated.

h) When 1 investigational product is administered, measure vital signs immediately before, within 10 minutes, and at 1 hour (± 10 minutes) after the infusion. If the subject experiences symptoms/signs of an infusion reaction, follow-up may be longer, as clinically indicated.

i) Performance status: ECOG for subjects > 16 years of age or Lansky score for subjects 12 to 16 years of age.

j) AEs by definition include SAEs, AEs of special interest, and nonserious AEs. All AEs, related and unrelated, will be recorded from the first dose of the first investigational product through 30 days after the last dose of investigational. In addition, any pregnancies or lactations in a female subject or the female partner of a male subject will be recorded through 120 days of the last dose of investigational product or 30 days following cessation of investigational product (if a new non-protocol NPC therapy is initiated), whichever is shorter.

k) During the inventory check and screening periods, any pre-treatment AEs considered by the investigator to be at least possibly related to study procedure(s) that occur from the time either ICF is signed until first dose of investigational product will be recorded.

l) During quarterly follow-up from 30 days after the last investigational product exposure, AEs considered by the investigator to be at least possibly related to either investigational product or study procedure(s) will be recorded. In addition, all SAEs, including AEs of special interest, occurring from the first dose of investigational product through 90 days following the last dose of investigational product, or through 30 days following cessation of investigational product if the subject initiates a new non-protocol therapy for EBV^+ NPC, whichever is shorter, will be recorded.

m) Hematology panel includes CBC with platelet count and differential.
Coagulation panel includes PT, aPTT, and INR.
Abbreviated chemistry panel includes serum creatinine, TBILI, ALT, AST, alkaline phosphatase, glucose (fasting), and tests of thyroid function (TSH, T3, and T4).
Full chemistry panel includes sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose (fasting), total calcium, albumin, total protein. and tests of thyroid function (TSH, T3, and T4).

n) Hematology, coagulation, and full chemistry panels.

o) Hematology and abbreviated chemistry panels.

p) Hematology and full chemistry panels.

CCI
CCI
CCI

t) **Cohort 1, checkpoint inhibitor-naïve subjects, and Cohort 2**: Archival tumor block/tumor sections if available (central laboratory).
Cohort 1, checkpoint inhibitor (PD-1/PD-L1) failed subjects only: Tumor/active site core needle, incisional or excisional biopsy will be obtained or archival sample will be provided; fine needle aspirate is not considered adequate for the purposes of this biopsy; hematology and coagulation panels must be performed prior to biopsy.

Evaluation	Inventory Check[a]	Screening[a]	Treatment/Consolidation Cycles with Observation (21-day)[a]				Maintenance Cycles with Observation (84-day)[a]			EOT Visit[a]	Quarterly Follow-up[a]
			Day 1	Day 8	Day 15	Day 21	Day 1	Days 21, 42, 63	Day 77		

u) **Cohort 1, checkpoint inhibitor (PD-1/PD-L1) failed subjects, and Cohort 2 (optional):** at least 1 day after Cycle 1 Day 8 and prior to Cycle 1 Day 15 core needle, incisional or excisional biopsy is required; hematology and coagulation panels must be performed prior to biopsy. NOTE: Fine needle aspirate is not considered adequate for the purposes of this biopsy.

v) Radiographic assessments include MRI or CT with contrast.

w) **Cohort 1, checkpoint inhibitor (PD-1/PD-L1) failed subjects only**: initial evidence of progressive disease with confirmation assessment for retrospective analysis at a central vendor.

x) Radiographic assessments will be performed at Screening and between Day 16 to Day 21 of Treatment/Consolidation Cycle 2 and beyond. During the Maintenance Phase, radiographic assessments will be performed on Day 77 (± 2 days) of each 84-day cycle. Radiographic assessments will also be performed at EOT and during Quarterly Follow-up for subjects who have achieved a CR, PR, or have SD but did not complete maintenance cycles or had disease progression.

y) Pembrolizumab will be administered prior to tabelecleucel. During treatment/consolidation cycles, pembrolizumab will be administered on Day 1 (unless the subject has confirmed disease progression) and tabelecleucel on Day 1, Day 8 and Day 15 of each cycle. During the maintenance cycles, pembrolizumab will be administered on Day 1, Day 21, Day 42, and Day 63, and tabelecleucel on Day 1 of each cycle. Tabelecleucel will be administered 1 hour (± 10 minutes) after the administration of pembrolizumab only if no infusion reactions related to pembrolizumab are observed/reported or in the case of such a reaction, the subject has recovered.

15.2 Detailed of the Study Design

After the inventory check and screening, all subjects will receive two 21-day treatment cycles of combination immunotherapy (tabelecleucel on Days 1, 8, and 15 with pembrolizumab on Day 1) and then undergo a response assessment at the Observation Visit (refer to Figure 1). Subjects will receive different subsequent treatment, consolidation, and/or maintenance cycles depending on their initial response assessment as follows:

- For CR or PR, refer to Section 15.2.1
- For an SD response, refer to Section 15.2.2
- For a uPD response, refer to Section 15.2.3
- for a cPD response, refer to Section 15.2.4

15.2.1 Complete or Partial Response after the Initial Two Treatment Cycles

A subject who achieves a CR or PR after the initial 2 treatment cycles will receive a Consolidation Cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 and pembrolizumab on Day 1 and have a response assessment at the Observation Visit (refer to Figure 1). Subsequent treatment is dependent on the response as follows:

- CR, PR, or SD: The subject will then receive maintenance cycles (84-day) of combination immunotherapy (pembrolizumab on Days 1, 21, 42, and 63 with tabelecleucel with the same HLA restriction on Day 1) and a response assessment at Day 77. Maintenance cycles will continue until disease progression, unacceptable toxicity, or a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given. The subject will then complete an End-of-Treatment visit with a response assessment at 30 days after the last dose of investigational product, and then enter Quarterly Follow-up for 12 months from last dose of investigational product or until disease progression.
- cPD: The subject will complete an End-of-Treatment visit (30 days after the last investigational product dose) and enter Quarterly Follow-up for 12 months after the last investigational product dose.

15.2.2 Stable Disease after the Initial Two Treatment Cycles

A subject who has SD after the initial 2 treatment cycles will receive Switch Therapy, ie a treatment cycle with tabelecleucel with a different HLA restriction, if an appropriately matched product is available on Days 1, 8, and 15 and pembrolizumab on Day 1 and then a response assessment at the Observation Visit (refer to Figure 1). Subsequent treatment is dependent on the response as follows:

- CR or PR: The subject will receive a consolidation cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 and pembrolizumab on Day 1 followed by a response assessment at the Observation Visit. The subject will then receive maintenance cycles (84-day) of combination immunotherapy (pembrolizumab on Days 1, 21, 42, and 63 with tabelecleucel with the same HLA restriction on Day 1) and a response assessment at Day 77. Maintenance cycles will continue until disease progression, unacceptable toxicity, or a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given. The subject will then complete an End-of-Treatment visit with a response assessment at 30 days after the last dose of investigational product, and then enter Quarterly Follow-up for 12 months from last dose of investigational product or until disease progression.

- SD: The subject will receive another treatment cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 and pembrolizumab on Day 1 followed by a response assessment at the Observation Visit. If the response is CR, PR, or SD, the subject will enter receive maintenance cycles. If the response is cPD, the subject will complete an End-of-Treatment visit (30 days after the last investigational product dose) and enter Quarterly Follow-up for 12 months after the last investigational product dose.

- uPD: The subject will receive another treatment cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 and pembrolizumab on Day 1 followed by a response assessment at the Observation Visit. As described above, if the response is CR, PR, or SD, the subject will receive maintenance cycles. If the response is cPD, the subject will complete an End-of-Treatment visit (30 days after the last investigational product dose) and enter Quarterly Follow-up for 12 months after the last investigational product dose.

- cPD: The subject will complete an End-of-Treatment visit (30 days after the last investigational product dose) and enter Quarterly Follow-up for 12 months after the last investigational product dose.

15.2.3 Unconfirmed Progressive Disease after the Initial Two Treatment Cycles

A subject who has uPD after the initial 2 treatment cycles will receive another treatment cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 and pembrolizumab on Day 1 and then a response assessment at the Observation Visit (refer to Figure 1). Subsequent treatment is dependent on the response as follows:

- CR or PR: The subject will then receive maintenance cycles (84-day) of combination immunotherapy (pembrolizumab on Days 1, 21, 42, and 63 with tabelecleucel with the same HLA restriction on Day 1) and a response assessment at Day 77. Maintenance cycles will continue until disease progression, unacceptable toxicity, or a total of 35 pembrolizumab infusions (including for treatment, consolidation, and maintenance) have been given. The subject will then complete an End-of-Treatment visit with a response assessment at 30 days after the last dose of investigational product, and then

enter Quarterly Follow-up for 12 months from last dose of investigational product or until disease progression.

- SD: The subject will receive Switch Therapy, ie a treatment cycle with tabelecleucel with a different HLA restriction, if an appropriately matched product is available on Days 1, 8, and 15 followed by a response assessment at the Observation Visit. If the response is CR, PR, or SD, the subject will receive maintenance cycles. If the response is cPD, the subject will complete an End-of-Treatment visit and enter Quarterly Follow-up for 12 months after the last investigational product dose.

- cPD: The subject will discontinue pembrolizumab and receive Switch Therapy, ie a treatment cycle with tabelecleucel with a different HLA restriction, if an appropriately matched product is available on Days 1, 8, and 15 followed by a response assessment at the Observation Visit. Subsequent treatment is dependent on the response as follows:

  – CR, PR, or SD: The subject will receive a consolidation cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 followed by a response assessment at the Observation Visit. The subject will then complete an End-of-Treatment visit with a response assessment at 30 days after the last dose of investigational product, and then enter Quarterly Follow-up for 12 months from last dose of investigational product or until disease progression.

  – cPD: The subject will then complete an End-of-Treatment visit (30 days after the last investigational product dose) and enter Quarterly Follow-up for 12 months after the last investigational product dose.

15.2.4 Confirmed Progressive Disease after the Initial Two Treatment Cycles

A subject who has a cPD will discontinue pembrolizumab and receive Switch Therapy, ie a treatment cycle with tabelecleucel with a different HLA restriction, if an appropriately matched product is available on Days 1, 8, and 15 followed by a response assessment at the Observation Visit (refer to Figure 1). Subsequent treatment is dependent on the response as follows:

- CR, PR, or SD: The subject will receive a consolidation cycle with tabelecleucel with the same HLA restriction on Days 1, 8, and 15 followed by a response assessment at the Observation Visit. The subject will then complete an End-of-Treatment visit with a response assessment at 30 days after the last dose of investigational product, and then enter Quarterly Follow-up for 12 months from last dose of investigational product or until disease progression.

- cPD: The subject will then complete an End-of-Treatment visit (30 days after the last investigational product dose) and enter Quarterly Follow-up for 12 months after the last investigational product dose.

15.3 Performance Status Scales

ECOG Performance Status for Subjects Aged > 16 Years

ECOG Grade	Status
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, eg, 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 self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Lansky Scoring for Subjects Aged 1 to 16 Years

Lansky Score	Status
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

15.4 Corticosteroid Approximate Equivalent Doses

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) (hours)
Short-Acting		
Cortisone	2.5	8–12
Hydrocortisone	2.0	8–12
Intermediate-Acting		
Methylprednisolone	0.4	18–36
Prednisolone	0.5	18–36
Prednisone	0.5	18–36
Triamcinolone	0.4	18–36
Long-Acting		
Betamethasone	0.06–0.075	36–54
Dexamethasone	0.075	36–54
Values reflect equivalent doses to prednisone 0.5 mg Source: http://www.globalrph.com/corticocalc.htm		

15.5 Description of the iRECIST Process for Assessment of Disease Progression

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 progressive disease 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 7 and Figure 2). This decision by the investigator should be based on the subject's overall clinical condition.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm progressive disease by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective IRR.

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 progressive disease by RECIST 1.1

Persistent iUPD

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

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

Additional 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 progressive disease threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be 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 progressive disease 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 progressive disease 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 7.1.2 and submitted to the central imaging vendor.

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 progressive disease 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 [40].

15.6 Severity Grading Scales

15.6.1 Acute GvHD

For acute GvHD, the clinical stage and severity should be evaluated according to the criteria outlined by the CIBMTR, as provided in Table 8 and Table 9, respectively.

Table 8 CIBMTR Acute GvHD: Clinical Stage

Stage	Skin	Liver	GI	Upper GI
	Body Surface Area	**Bilirubin (mg/dL)**	**Diarrhea (mL/day)**	**Nausea**
1	< 25%	2–3	500–1000	Present
2	25–50%	3.1–6	1000–1500	—
3	Generalized erythroderma	6.1–15	> 1500	—

Table 8 CIBMTR Acute GvHD: Clinical Stage

Stage	Skin Body Surface Area	Liver Bilirubin (mg/dL)	GI Diarrhea (mL/day)	Upper GI Nausea
4	Bullae	> 15	Pain ± ileus	—

Source: https://www.cibmtr.org/meetings/materials/crpdmc/pages/fall10Arora.aspx

Table 9 CIBMTR Acute GvHD: Severity Grading

Overall Acute GvHD Grade	Skin Stage	Liver Stage	GI Stage	Upper GI Stage
I	1–2	0	0	0
II	1–3	1	1	1
III	2–3	2–4	2–3	—
IV	4	—	4	—

Note: The clinical stage is ascertained per criteria in Table 8.
Source: https://www.cibmtr.org/meetings/materials/crpdmc/pages/fall10Arora.aspx

15.6.2 Chronic GvHD

For chronic GvHD, severity (ie, mild, moderate, severe) is defined by a global scoring algorithm described by the NIH consensus criteria [20]. The severity of the chronic GvHD event is then mapped to appropriate CTCAE grade.