A Phase 1/2 Trial Investigating the Safety and Efficacy of Autologous TAC T Cell Monotherapy, and TAC T Cells in Combination with Pembrolizumab, in Relapsed HER2-Positive Solid Tumors

Protocol Number: TAC01-HER2-03 (TACTIC-2)

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Version: 6.0

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This study will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable state, local, and federal regulatory requirements.

INVESTIGATOR PROTOCOL SIGNATURE PAGE

A Phase 1/2 Trial Investigating the Safety and Efficacy of Autologous TAC T Cell Monotherapy, and TAC T Cells in Combination with Pembrolizumab, in Relapsed HER2-Positive Solid Tumors (TACTIC-2)

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the Declaration of Helsinki, the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice, US FDA regulations, IRB/IEC requirements, all national, state, and local laws and/or requirements of pertinent regulatory authorities.

_____

Investigator Printed Name

_____ _____

Investigator Signature Date Signed

SPONSOR SIGNATURE PAGE

A Phase 1/2 Trial Investigating the Safety and Efficacy of Autologous TAC T Cell Monotherapy, and TAC T Cells in Combination with Pembrolizumab, in Relapsed HER2-Positive Solid Tumors

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signatures:	Date Signed:
_____	_____
Deyaa Adib, MD Chief Medical Officer	
_____	_____
Peter Shabe Statistician	
_____	_____
Kara Moss Sr. Director of Clinical Operations	

PROTOCOL SYNOPSIS

Protocol Number: TAC01-HER2-03 (TACTIC-2)	**Product Name**: TAC01-HER2 (TAC T Cells)
Protocol Title: A Phase 1/2 Trial Investigating the Safety and Efficacy of Autologous TAC T Cell Monotherapy, and TAC T Cells in Combination with Pembrolizumab, in Relapsed HER2-Positive Solid Tumors	
Sponsor: Triumvira Immunologics, Inc. (Triumvira)	**Study Phase**: 1/2

Study Rationale:

Despite recent therapeutic developments for patients with advanced, metastatic, unresectable human epidermal growth factor receptor 2 positive (HER2+) solid tumors, a significant unmet medical need still exists, especially in solid tumors where there are no approved HER2-targeted therapies and/or in tumors with low or intermediate HER2 expression. The T cell antigen-coupler (TAC) technology is a novel approach to modifying a patient's own T cells, herein referred to as TAC T cells, and using them in the treatment of solid tumors. TAC T cells are produced through genetic engineering, incorporating TAC receptors into a patient's own T cells. This redirects these enhanced T cells to specific cancer antigens, and upon recognition, activates them through the natural signaling pathways of the endogenous T cell receptor (TCR).

In the TAC01-HER2 product, TAC T cells use the HER2 antigen, which is present on the surface of cancer cells, to recognize and eradicate tumor cells. Promising outcomes have been observed in mouse models, with TAC T cells accumulating within solid tumors, resulting in a robust antitumor efficacy profile paired with a favorable safety profile. TAC T cells can also persist for extended periods of time in mice and protect the host from tumor regrowth. Consequently, it is hypothesized TAC01-HER2 monotherapy will be safe and effective in treating patients with HER2+ solid tumors and can provide a significant therapeutic benefit in an area of high unmet medical need.

Phase 1 will evaluate escalating single doses of TAC01-HER2 (on Day 1) as a monotherapy, and in combination with a fixed pembrolizumab approved prescription dose (200 mg every 3 weeks [Q3W]) beginning on either Day 21 or Day 14 to identify the recommended Phase 2 doses (RP2Ds) for TAC01-HER2 treatment in subjects with HER2+ solid tumors, who have progressed after 2 prior lines of therapy.

In vitro nonclinical studies conducted by Triumvira suggest that TAC T cells specifically engage with HER2+ cancer cells. As part of this T cell activation process, TAC T cells, similar to any other activated T cell, can induce the expression of programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1), which can consequently lead to reduced TAC T cell activity. Blocking PD-1 signaling via an anti-PD-1 checkpoint blockade, such as pembrolizumab, can counteract this inhibitory function. Therefore, these observations highlight the importance of evaluating the combination of TAC01-HER2 treatment with PD-1 blockade to potentially enhance the antitumor activity of administered TAC T cells. Attenuating the eventual exhaustion of TAC T cells may also facilitate the recruitment of endogenous polyclonal immune cells to overcome tumor heterogeneity and to prevent antigen escape (Grosser 2019). Mechanistically, this occurs through first treatment with TAC01-HER2, followed by pembrolizumab to block PD-L1 and PD-L2 ligands on cancer cells from binding to PD-1 receptors on resultant circulating TAC T cells.

In addition to 3+ HER2 tumors, subjects with low-HER2 expressing solid tumors (i.e., 2+ and 1+) will also be allowed to participate in this trial. These subjects constitute an area of high unmet medical need, e.g., 60% of all breast cancer patients have low-HER2 expressing tumors (Modi 2022). Nonclinical studies have demonstrated that TAC T cells are equally effective in eliciting antitumor activity regardless of HER2 expression levels (Figure 7) and are active in killing tumor cells that are resistant to trastuzumab and pertuzumab. In addition, trastuzumab deruxtecan, a HER2-targeting antibody drug conjugate, has recently demonstrated significant success in treating low HER2-expressing tumors in breast cancer patients (i.e., with an objective response rate [ORR] of 37.0% in a Phase 1B trial [Modi 2020] and 52.3% in the Destiny Breast04 Phase 3 trial [Modi 2022]), with a median duration of response (DOR) of 10.7 versus 6.8 months (in the Phase 3 trial) for trastuzumab deruxtecan treatment vs the physician's choice of chemotherapy (Modi 2022).

In conclusion, HER2 overexpression and/or amplification is observed in breast, gastric, lung, pancreatic, salivary, vaginal, endometrial, gall bladder, colorectal, and cervical cancers. It activates numerous oncogenic signaling pathways (e.g., PI3K/AKT and Ras/Raf/ERK) resulting in improved malignant cell survival, proliferation,

migration, and resistance to immunotherapy (Vafaei 2022). HER2-targeted therapies continue to evolve in treating patients with varying levels of HER2 expression. However, continued advances using novel targeted therapies are still needed to treat patients more effectively and with fewer side effects.

Study Objectives:

Objectives	Endpoints
Primary	
Phase 1: To evaluate the safety of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	Incidence of dose limiting toxicities (DLTs) Type, frequency, and severity of adverse events (AEs) (including clinically significant laboratory abnormalities).
Phase 2: To evaluate the clinical activity of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	ORR DOR Overall survival (OS) Disease control rate (DCR) Progression-free survival (PFS) or Time to progression (TTP) Investigator-assessed imaging using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
Secondary	
Phase 1: To determine the maximum tolerated dose (MTD) or RP2D for TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	Incidence of DLTs
Phase 2: To evaluate the safety of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	Type, frequency, and severity of AEs (including clinically significant laboratory abnormalities).
Phase 1 and Phase 2: To characterize the pharmacokinetic (PK) profile of TAC01-HER2 in subjects with HER2+ solid tumors	Maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), and area under the concentration time curve (AUC) of TAC T cells Duration of persistence of TAC T cells
Phase 1: To evaluate the clinical activity of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	ORR DOR OS DCR PFS or TTP Investigator-assessed imaging using RECIST 1.1
Phase 1 and Phase 2: To evaluate the immunogenicity of TAC01-HER2 monotherapy and pembrolizumab combination therapy and to assess potential impacts on PK exposure and biological activity	Immunogenicity of TAC T cells and pembrolizumab

Phase 1 and Phase 2: To investigate candidate efficacy biomarkers and anti-tumor activity of TAC T cells utilizing pre- and post-treatment tumor biopsies	Cytokines and TAC copies/µg genomic DNA (gDNA)
Exploratory	
Phase 1 and Phase 2: To explore biomarkers that may predict pharmacologic activity or response to TAC01-HER2 monotherapy and pembrolizumab combination therapy	Characterize T cells and correlate with clinical outcomes Describe profile of soluble immune factors and relationship to cytokine release syndrome (CRS), neurotoxicity, and TAC T cell engraftment

Study Design:

This is a first-in-human study investigating TAC01-HER2 monotherapy and combination therapy with pembrolizumab to evaluate the safety, MTD or RP2D, PK parameters, and clinical activity in subjects with HER2+ solid tumors. During the Phase 1 portion of the study, increasing dose levels of TAC01-HER2 monotherapy will be evaluated first using the keyboard design method:

Dose Level	TAC T Cells/kg body weight (Single Dose on Day 1)
-1	$6 – 8 \times 10^4$
1 (starting dose)	$1 – 3 \times 10^5$
2	$6 – 8 \times 10^5$
3	$1 – 3 \times 10^6$
4	$6 – 8 \times 10^6$

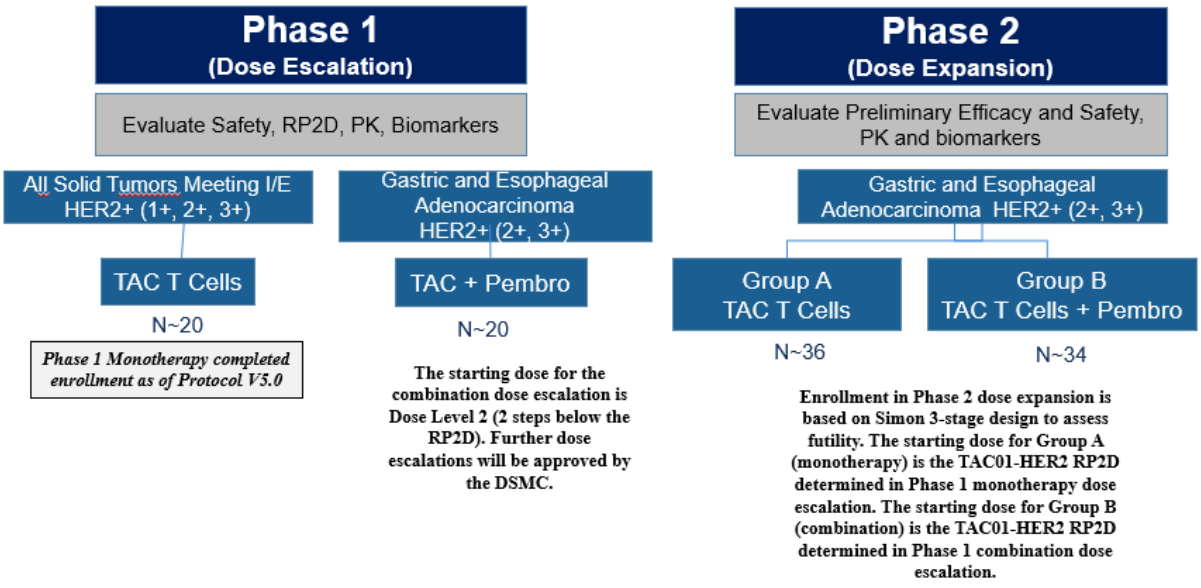
Once monotherapy has been investigated, the safety data reviewed by the Data Safety Monitoring Committee (DSMC), and the RP2D is determined, combination therapy can begin in parallel with monotherapy dose expansion starting at a dose level that is 2 steps below the RP2D for TAC01-HER2. The RP2D has been determined by the DSMC to be Dose Level 4. Accordingly, the starting dose level will be Dose Level 2. The following TAC T cell dose levels will be investigated in the combination arm.

Dose Level	TAC T Cells/kg body weight (Single Dose on Day 1)	Pembrolizumab
1	$1 – 3 \times 10^5$	200 mg Q3W
2 (starting dose)	$6 – 8 \times 10^5$	200 mg Q3W
3	$1 – 3 \times 10^6$	200 mg Q3W
4	$6 – 8 \times 10^6$	200 mg Q3W

Subjects will be allocated to the group that allows the subject to start their treatment regimen in the shortest timeframe. Priority to enrollment will be for the combination dose escalation arm, with the following exceptions: within the safety gate interval, during DLT observation period, subject and Investigator preference, and if subject does not meet criteria to receive pembrolizumab.

As an additional safety precaution, the first combination cohort will treat 3 subjects with TAC T cells and administer pembrolizumab on Day 21. After review of safety data by the DSMC and in the absence of DLTs, an additional 3 subjects will be treated at this same initial combination dose level, with pembrolizumab administered on Day 14. Based on the results of these 6 subjects, the DSMC will either recommend Day 21 or Day 14 for the start of pembrolizumab administration in all subsequent combination cohorts, followed by administration of pembrolizumab 200 mg Q3W for up to 2 years.

The overall study design is outlined below:



Abbreviations: DSMC=Data Safety Monitoring Committee; HER2=human epidermal growth factor receptor 2; I/E=inclusion/exclusion; N=number of subjects; Pembro=pembrolizumab; PK=pharmacokinetics; RP2D=recommended Phase 2 dose; TAC=T cell antigen coupler.

Phase 1 will evaluate increasing dose levels of TAC01-HER2 as a monotherapy, and in combination with pembrolizumab, to identify RP2Ds in subjects with HER2+ solid tumors who have progressed after 2 prior lines of therapy.

In Phase 2, dose expansion groups will further evaluate the safety, clinical activity, and PK of the RP2D for TAC01-HER2 in HER2+ gastric and esophageal adenocarcinoma who have progressed after 2 and no more than 4 prior lines of therapy in 2 groups: **Group A** (TAC01-HER2 monotherapy) and **Group B** (TAC01-HER2 + pembrolizumab). Central laboratory confirmation of HER2+ by immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH) will be conducted.

In Phase 2, a second dose (monotherapy arm only) may be administered (see Section 3.4 for additional details and Section 4.3 for eligibility criteria of second dose).

Upon enrollment, subjects will undergo leukapheresis to obtain T cells for TAC01-HER2 manufacture. Subjects may receive bridging anticancer therapy, after leukapheresis and before lymphodepleting chemotherapy (LDC) if deemed necessary by the Investigator. Bridging therapies must be discontinued at least 14 days prior to initiation of lymphodepletion, and subjects must continue to meet eligibility criteria pertaining to adequate organ function (except hematologic parameters), active infections, pregnancy, measurable disease confirmed by repeat imaging, and medication washout before initiation of lymphodepletion. If TAC01-HER2 cannot be manufactured from the first leukapheresis product, additional leukapheresis may be allowed after consultation with Triumvira.

Upon the successful manufacturing of TAC01-HER2, subjects will enter the treatment phase. In the monotherapy arm, treatment will include LDC followed by a single dose of TAC01-HER2 administered intravenously (IV) on Day 1. In the combination arm, treatments will include LDC, a single dose of TAC01-HER2 administered IV on Day 1, and pembrolizumab 200 mg administered IV Q3W starting on Day 21 or Day 14 based on recommendations from the DSMC.

Subjects who receive 1 dose and subjects who receive combination therapy will follow procedures described in Appendix A1 and Appendix A2, respectively, for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up. Radiographic disease assessments for progressive disease (PD) and other responses in single-dose subjects will occur at Day 29±2 days, then Q8W±2W for Year 1 and Q12W±2W for Year

2. If a subject who receives 1 dose has initial PD on the Day 29±2W scan, a confirmation scan should occur 28 days (± 7 days) later to confirm the initial PD was not a tumor flare.

Subjects who receive 2 doses will follow procedures described in Appendix B for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up. Assessments for PD will occur on Day 29±2 days after the first dose on Day 1, then Q8W±2W until the second dose is administered. Once the second dose is administered (i.e., Day X), scans will be performed on Day X + 28±2 days, Q8W±2W after Day X for 1 year, and then Q12W±2W after Day X for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up.

If a subject has confirmed PD 3 months after the first dose, starts a new anticancer therapy, or is unwilling or unable to continue the respective procedures indicated in Appendix A1, Appendix A2, or Appendix B, then the subject will transition to the long-term follow-up (LTFU) protocol.

The LTFU protocol has a reduced schedule of events that complies with regulatory requirements for follow-up and does not include radiographic disease assessments. After study completion, subjects will be followed for survival, long-term toxicity, and viral vector safety to be monitored for up to 15 years.

Dose Limiting Toxicities:

Toxicities will be evaluated and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (National Cancer Institute 2020), and CRS and neurotoxicity per American Society for Transplantation and Cellular Therapy (ASTCT; Lee 2019) Consensus Grading as in Appendix D.

In the monotherapy arm, a DLT is defined as:

- Any Grade 4 or 5 event determined by the Investigator to be related to the investigational product, and not attributable to the underlying disease or LDC, with the exception of Grade 4 laboratory abnormalities (such as electrolyte abnormalities) that may be at least possibly related to the investigational product but are rapidly reversible or correctable without substantial safety concerns.
- Grade ≥3 TAC T cell-associated acute infusion reactions persisting for ≥24 hours
- Grade ≥3 TAC T cell-associated CRS or neurotoxicity persisting for ≥72 hours
- Grade ≥3 cardiovascular or pulmonary toxicity persisting for ≥72 hours
- Grade ≥3 immune-related toxicities (i.e., colitis, nephritis, hepatitis, myocarditis, hypophysitis, salivary gland toxicity, etc.)
- Grade ≥3 organ toxicities or non-hematologic toxicities that do not improve to Baseline within 7 days
- Clinically consequential Grade ≥3 neutropenia or thrombocytopenia lasting ≥30 days from TAC01-HER2 administration. Clinically consequential is defined as febrile neutropenia, serious infection, or bleeding events.

In the combination arm, a DLT is defined as:

Definitions from the monotherapy arm that also apply to the combination arm:

- Any Grade 4 or 5 event determined by the Investigator to be related to the investigational product, and not attributable to the underlying disease or LDC, with the exception of Grade 4 laboratory abnormalities (such as electrolyte abnormalities) that may be at least possibly related to the investigational product but are rapidly reversible or correctable without substantial safety concerns.
- Grade ≥3 TAC T cell-associated acute infusion reactions persisting for ≥24 hours
- Grade ≥3 TAC T cell-associated CRS or neurotoxicity persisting for ≥72 hours
- Grade ≥3 cardiovascular or pulmonary toxicity persisting for ≥72 hours
- Grade ≥3 immune-related toxicities (i.e., colitis, nephritis, hepatitis, myocarditis, hypophysitis, salivary gland toxicity, etc.)
- Grade ≥3 organ toxicities or non-hematologic toxicities that do not improve to Baseline within 7 days

Additional definitions of DLTs applicable to the combination arm:

- Any event that meets the definition of a DLT for the monotherapy arm that occurs before pembrolizumab administration, will prevent any pembrolizumab administration (subject will be discontinued from the combination arm and will follow the monotherapy schedule of events in Appendix A1).
- Grade 4 nonhematologic toxicity (not laboratory)
- Any new or worsening clinically significant Grade ≥3 neutropenia or thrombocytopenia lasting ≥7 days

that develops ≤3 days after pembrolizumab administration despite best institutional corrective treatment measures

- Any Grade 4 hematological toxicity lasting ≥7 days after pembrolizumab administration despite best institutional corrective treatment measures
- 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 participant
  - The abnormality leads to hospitalization
  - 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 absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°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 participant to discontinue treatment during Cycle 1
- Grade 5 toxicity

DLT Evaluation Periods and Relatedness:

In the monotherapy arm, DLTs will be assessed from the time of the TAC01-HER2 infusion on Day 1 through 28 days post dose. The DLT evaluation period may be extended through 42 days post dose should clinically consequential (i.e., events associated with febrile neutropenia, serious infections, or bleeding) Grade ≥3 neutropenia or thrombocytopenia occur.

In the combination arm, DLTs will be assessed from the time of the TAC01-HER2 dose (Day 1) through Day 42 for cohorts that dosed pembrolizumab on Day 21, and through Day 35 for cohorts that dosed pembrolizumab on Day 14. In both scenarios, DLTs will include assessments over 1 cycle of pembrolizumab treatment (or 21 days after the initial dose of pembrolizumab).

DLTs that occur after TAC01-HER2 administration but before pembrolizumab treatment will be attributable to TAC01-HER2. DLTs that occur after pembrolizumab administration will be attributable to both study treatments. Since TAC01-HER2 is a single dose infusion, all DLTs or other adverse reactions observed after pembrolizumab administration will follow the guidelines for dose modification or discontinuation criteria listed in Appendix H and Appendix I.

The dose elimination rule in the keyboard design will be used as a stopping boundary for toxicity. Specifically, enrollment will be stopped if data indicate more than a 95% chance that the DLT rate exceeds 30%, corresponding to a strong signal that the RP2D previously selected was in error.

Inclusion Criteria:

Subjects must meet all the following criteria to participate in this study:

1. Signed, written informed consent obtained prior to any study specific procedures.
2. Age ≥18 years at the time of informed consent.
3. **For Phase 1 and Phase 2:**
   - Phase 1 monotherapy: HER2 1+, 2+, 3+ by IHC by central laboratory confirmation
   - Phase 1 combination: therapy: HER2 2+, 3+ by IHC and FISH by central laboratory confirmation
   - Phase 2 monotherapy (Group A): HER2 2+, 3+ by IHC and FISH by central laboratory confirmation
   - Phase 2 combination therapy (Group B): HER2 2+, 3+ by IHC and FISH by central laboratory

confirmation

In both phases, subjects who are HER2+ via recent (preferably after last line of therapy or within 1 year) tissue biopsy local laboratory results using IHC, FISH, or next generation sequencing (NGS) assays may also be enrolled, as long as a recent (preferably fresh or archival within 1 year) tissue biopsy sample is available for central laboratory HER2+ confirmation after enrollment and/or after starting TAC01-HER2. In the instance of discordant results between central and local laboratories (i.e., central laboratory results are negative with regards to IHC or FISH), the subject will still be considered evaluable for safety and evaluation of DLTs. In the instance of discordant results between central and local laboratories, the subject may be replaced in Phase 2.

Central laboratory confirmation of HER2+ tumor samples will occur by one of the following methods (in order of priority, also see Section 7.2.3.1):

a. A fresh tumor tissue sample, if clinically feasible and safe
b. An archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1)
c. A liquid biopsy to examine circulating tumor cells
d. If a, b, or c are not obtainable, the most recent archival sample available regardless of when it was obtained during prior lines of therapy

Fine needle aspirations, or brushing and scraping cytology samples, are not acceptable at Baseline or Screening. Since Phase 2 will be evaluating efficacy and since HER2 status often changes on progression after HER2-targeted therapies (e.g., trastuzumab), it is strongly recommended a fresh tumor tissue sample be obtained, if clinically feasible and safe, along with the corresponding pathology report for histological disease diagnosis confirming HER2-protein expression on the tumor cell surface.

4. Histologically confirmed advanced, metastatic, unresectable solid tumors (regardless of PD-L1 expression levels; Phase 1) and histologically confirmed advanced, metastatic, unresectable gastric or esophageal adenocarcinoma (regardless of PD-L1 expression levels for Phase 1 combination therapy and Phase 2) after at least 2 prior lines of therapy (Phase 1) or after at least 2 and no more than 4 prior lines of therapy (Phase 2). For the completed Phase 1 monotherapy subjects, HER2+ incurable malignancies for which no standard-of-care HER2 targeted therapy exists were enrolled regardless of the number of prior treatment lines, as long as in the opinion of the investigator the subject would be unlikely to tolerate or derive clinically meaningful benefit from other available treatment options. For breast cancer subjects, both prior lines of therapy must have included HER2-targeted agents per current standard-of-care. Subjects in the Phase 1 combination arm and Phase 2 can be enrolled if they have received less than 2 prior lines of therapy if, in the opinion of the investigator, the subject would not derive meaningful clinical benefit from an additional line of therapy.

   Subjects with solid tumors with genetic alterations and mutations (such as BRAF, BRCA, EGFR mutations, and ALK translocation) where approved targeted therapies were available to their specific cancers must have been previously treated with such approved therapies, or refused such approved targeted therapy for their cancers, prior to enrollment, or in the opinion of the investigator would be unlikely to tolerate or derive clinically meaningful benefit from these standard-of-care therapies.
5. Measurable disease per RECIST 1.1 at time of enrollment. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at Screening.
7. Life expectancy of at least 12 weeks.
8. Adequate organ and bone marrow reserve function prior to leukapheresis for monotherapy and combination arms can be found in Tables A and B, respectively.
9. Recovery to Grade ≤1 or Baseline for any toxicities due to previous therapy.
   a. If a subject received major surgery, they must have recovered adequately from the procedure and/or complications from the procedure prior to starting TAC01-HER2 therapy.
   b. Toxicity that has not recovered to Grade ≤1 is allowed if it meets the inclusion requirements for laboratory parameters.
   c. <u>For the combination arm only:</u> Subjects with Grade ≤2 neuropathy may be eligible, as may subjects with endocrine-related Grade ≤2 AEs requiring treatment or hormone replacement.
10. Adequate vascular access for leukapheresis as per institutional guidelines
11. For women physiologically capable of becoming pregnant, agreement to use highly effective methods of

contraception starting 28 days prior to study treatment and for 1 year after the TAC01-HER2 dose. For men who have partners physiologically capable of becoming pregnant, agreement to use an effective barrier contraceptive method and refrain from donating sperm during study treatment and for 1 year after the TAC01-HER2 dose.

12. Subjects who are hepatitis B surface antigen (HBsAg) positive are eligible if they have received hepatitis B virus (HBV) antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to enrollment. Note: Subjects should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.
13. Subjects with history of hepatitis C virus (HCV) infection are eligible if HCV viral load is undetectable at Screening. Note: Subjects must have completed curative anti-viral therapy at least 4 weeks prior to enrollment.

Table A: Adequate Organ Function Laboratory Values for the Monotherapy Arm

System	Laboratory Value
Hematologic [a]	
Absolute neutrophil count (ANC)	≥1,000.0/µL
Absolute lymphocyte count (ALC)	≥450.0/µL [d]
Platelets [a]	≥75,000.0/µL
Hemoglobin [a]	≥8.0 g/dL
Renal	
Creatinine **AND** Estimated glomerular filtration rate (eGFR) [b] **OR** measured creatinine clearance [c]	≤1.5 X upper limit of normal (ULN) **AND** ≥60.0 mL/min/1.73 m^2 **OR** ≥40 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 X ULN **OR** ≤3 x ULN in the presence of liver metastases **OR** In subjects with known Gilbert's disease, serum total bilirubin <3 mg/dL
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5 X ULN or, If liver metastases present ≤5 X ULN
Alkaline phosphatase (AP)	≤2.5 X ULN or ≤5 x ULN for subjects with liver metastases or bone lesions.
Coagulation	
International normalized ratio (INR) or prothrombin time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Respiratory	
Adequate respiratory reserve	Grade 0 or 1 dyspnea and peripheral oxygen (O_2) saturation of ≥92% on room air
Cardiac	
Echocardiogram (ECHO) or multigated acquisition (MUGA) Scan	Left ventricular ejection fraction (LVEF) ≥45%

[a] Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support.
[b] eGFR should be calculated per institutional standard.
[c] Creatinine clearance should be calculated per institutional standard.
[d] Subjects with an ALC below 450.0/µL should be discussed with Triumvira's Medical Monitor for assessment of suitability for high volume leukapheresis based on the subject's tolerance, underlying malignancy, and any latent effects from prior antineoplastic therapies.

Table B: Adequate Organ Function Laboratory Values for the Combination Arm

System	Laboratory Value
Hematologic [a]	
Absolute neutrophil count (ANC)	≥1500/µL
Absolute lymphocyte count (ALC)	≥450.0/µL [d]
Platelets	≥100,000.0/µL
Hemoglobin [a]	≥9.0 g/dL or ≥5.6 mmol/L [a]
Renal	
Creatinine **AND** Estimated glomerular filtration rate (eGFR) [b] **OR** measured creatinine clearance [c]	≤1.5 X upper limit of normal (ULN) **AND** ≥60.0 mL/min/1.73 m^2 **OR** ≥40 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 X ULN **OR** ≤3 x ULN in the presence of liver metastases **OR** In subjects with known Gilbert's disease, serum total bilirubin <3 mg/dL
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5 X ULN or, If liver metastases present ≤5 X ULN
Alkaline phosphatase (AP)	≤2.5 X ULN or ≤5 x ULN for subjects with liver metastases or bone lesions.
Coagulation	
International normalized ratio (INR) or prothrombin time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Respiratory	
Adequate respiratory reserve	Grade 0 or 1 dyspnea and peripheral oxygen (O_2) saturation of ≥92% on room air
Cardiac	
Echocardiogram (ECHO) or multigated acquisition (MUGA) Scan	Left ventricular ejection fraction (LVEF) ≥45%

[a] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥approximately 3 months).
[b] eGFR should be calculated per institutional standard.
[c] Creatinine clearance should be calculated per institutional standard.
[d] Subjects with an ALC below 450.0/µL should be discussed with Triumvira's Medical Monitor for assessment of suitability for high volume leukapheresis based on the subject's tolerance, underlying malignancy, and any latent effects from prior antineoplastic therapies.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Intolerant to any component of TAC01-HER2.
2. Prior treatment with any of the following:
   a. Adoptive cell transfer of any kind, including chimeric antigen receptor (CAR) T cells
   b. Gene therapy
3. Investigational medicinal product within 5 half-lives or 21 days prior to leukapheresis, whichever is shorter.
4. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccines are allowed.
5. Monoclonal antibody (mAb), including PD-1 and PD-L1, therapies within 21 days prior to leukapheresis.
6. Radiation within 28 days prior to leukapheresis. Palliative radiation is allowed up to 14 days prior to leukapheresis if additional non-irradiated lesions are present.
7. Chemotherapy or targeted small molecule therapy within 14 days prior to leukapheresis, or within 7 days prior to leukapheresis for erlotinib, gefitinib, afatinib, crizotinib, or tucatinib.
8. Colony stimulating factors, including granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin, and other hematopoietic cytokines, within 14 days prior to leukapheresis.
9. Immunosuppressive medication within 14 days and corticosteroid treatment <72 hours prior to leukapheresis, except for physiological replacement doses (<12 mg/m^2/24 hours) of hydrocortisone or equivalent and topical or inhaled steroids.
10. History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
11. Active inflammatory neurological disorders (e.g., Guillain-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis).
12. Active autoimmune disease (e.g., lupus, rheumatoid arthritis, Sjogren's syndrome) requiring systemic treatment (i.e., disease modifying agents, corticosteroids, or immunosuppressive drugs) in the past 2 years. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
13. Active or uncontrolled hepatitis B or C (HCV ribonucleic acid [RNA] positive) infection or any history of or active human immunodeficiency virus (HIV) infection.
14. Uncontrolled, acute, or life-threatening bacteria, viral, or fungal infection. Subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible if no evidence of active infection, this includes COVID subjects.
15. Class III or IV heart failure (as defined by the New York Heart Association [NYHA]), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease within 6 months prior to Screening.
16. Cardiac arrhythmia not controlled by medical management.
17. Clinically significant thrombotic events within 6 months prior to leukapheresis and/or inability to stop anticoagulation for at least 2 half-lives prior to TAC01-HER2 infusion without compromising a subject's health.
18. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, non-metastatic squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
19. Pregnant or nursing (lactating). Females physiologically capable of becoming pregnant must have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test result at Screening and within 48 hours prior to initiating LDC.
20. As determined by the Investigator, any uncontrolled medical, psychological, familial, sociological, or

geographical condition(s) that do(es) not permit compliance with the protocol.

21. Is currently participating in or has participated in a study using an investigational device within 4 weeks prior to the first dose of study treatment.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate, in the opinion of the treating investigator.
23. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Combination Arm Only Specific Exclusions:

24. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
25. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., cytotoxic t-lymphocyte-associated protein 4 [CTLA-4], OX-40, cluster of differentiation [CD]137), and was discontinued from that treatment due to a Grade 3 or higher immune-related AE (irAE).
26. Removed; combined with exclusion #10 (protocol Version 6.0).
27. Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of trial treatment.
28. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
29. Has history of an allogeneic stem cell transplant or a solid organ transplant.
30. Has a history of radiation pneumonitis. (Note: Cannot receive prior radiotherapy within 2 weeks of start of pembrolizumab. Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation [≤2 weeks of radiotherapy] to non-CNS disease; see Section 7.3.3).

Investigational Product, Dosage, and Mode of Administration:

Product Name and Description:

TAC01-HER2 is an autologous T cell product comprising T cells expressing the TAC-HER2, a chimeric receptor that is genetically engineered into T cells via lentiviral transduction to furnish T cells with 2 main functions: (i) redirection to and specific recognition of HER2+ cells, and (ii) T cell activation via the endogenous TCR.

Structure:

The chimeric TAC-HER2 receptor consists of 3 main functional domains: (i) an extracellular HER2-binding domain provided by the H10-2-G3 designed ankyrin repeat protein (DARPin); (ii) an extracellular TCR/CD3ε-binding domain (huUCHT1 scFv); and (iii) a membrane-anchoring domain that consists of the transmembrane and cytoplasmic domains of CD4. The HER2-binding domain is designed to bind to the HER2 surface antigen expressed on HER2+ cells, including HER2+ non-malignant cells. The TCR/CD3ε binding domain is designed to recruit the endogenous TCR complex. The cytoplasmic tail includes the lymphocyte-specific protein tyrosine kinase (Lck) binding site of CD4 which is expected to contribute to T cell activation upon recruitment of the TCR.

Dosage Form:

The TAC01-HER2 product is a suspension of genetically modified autologous T cells expressing TAC-HER2 for infusion (i.e., HER2-targeted TAC T cells) containing 10% dimethyl sulfoxide (DMSO) in approximately 20 mL.

Administration:

TAC01-HER2 will be administered as a single IV infusion approximately 72 hours after completion of LDC. LDC will preferentially consist of 3 consecutive days of fludarabine (30 mg/m^2 IV) or clofarabine (52 mg/m^2 IV) and cyclophosphamide (300 mg/m^2 IV) with or without mesna IV. Central venous access is recommended for the infusion of TAC01-HER2.

If fludarabine or clofarabine is unavailable (due to national shortages), subjects can be treated with 3 consecutive days of cyclophosphamide (300 mg/m^2 IV) with or without mesna IV or with bendamustine 90 mg/m^2 daily for

2 days for subjects who cannot tolerate cyclophosphamide.

The dose intensity of either the primary (fludarabine or clofarabine + cyclophosphamide) or backup (cyclophosphamide or bendamustine) regimens can be modified based on a subject's complete blood count (CBC) and creatinine clearance, upon discussion with the Medical Monitor.

Pembrolizumab:

Pembrolizumab 200 mg IV will be administered Q3W starting on Day 21 or Day 14 from administration of the TAC T cells. The initial combination dose-escalation cohort will have pembrolizumab administered on Day 21. For all remaining cohorts, pembrolizumab will be administered on Day 14 if no DLTs or safety issues are identified (as approved by the DSMC). The Day 14 time point was chosen based on nonclinical in vivo data showing maximal TAC T cell expansion in the tumor around and after Day 7 post IV administration. The Day 21 time point for the initial pembrolizumab administration in the combination arm was chosen as an additional safety precaution to allow an extra week for any TAC T cell-related AEs to emerge and be managed as appropriate.

Dose modifications and discontinuations will follow the guidelines described in Appendix H and Appendix I.

Disease Response Assessments:

Disease assessments should be performed using computed tomography (CT) (or magnetic resonance imaging [MRI] if indicated). Scans will be reviewed and assessed locally by the Investigator and radiology using RECIST 1.1. The same imaging technique should be used for a subject throughout the study, and lesions detected at Baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. The Investigator may perform scans in addition to scheduled study scans if clinically indicated per the Investigator's discretion.

Safety Assessments:

AEs will be assessed throughout the study according to CTCAE Version 5.0 (National Cancer Institute 2020), and CRS and neurotoxicity per ASTCT (Lee 2019) Consensus Criteria. AEs, serious adverse events (SAEs), and laboratory abnormalities (type, frequency, and severity) will be collected.

Potential TAC01-HER2 cell related toxicities may include infusion reactions, CRS, neurotoxicity, macrophage activation syndrome, and tumor lysis syndrome (TLS); with the list of these risks being updated during the study based on any observed safety signals. Replication-competent lentivirus (RCL) and, if positive, follow-up viral vector sequence, testing will be performed at specified time points during the study using polymerase chain reaction (PCR)-based assays.

Potential pembrolizumab related toxicities may include fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism. Immune-mediated and infusion-related adverse reactions, which may be severe or fatal, can occur in any organ system or tissue for which monitoring for early identification and management is required per Appendix H and Appendix I, respectively.

In conclusion, there is no toxicity overlap to be expected between TAC01-HER2 cell therapy and pembrolizumab.

Other Assessments:

PK Assessments: Assessment of TAC T cell expansion and persistence in blood will be determined by quantitative polymerase chain reaction (qPCR) to detect the TAC-HER2 transgene and by flow cytometry to enumerate the number and immunophenotypic TAC T cells.

Biomarker Assessments: Biomarker assessments will be performed to evaluate HER2+ tumor status, and immune system characteristics that may be associated with TAC T cell toxicity, clinical activity, and resistance mechanisms to TAC01-HER2 treatment.

Statistical Methods:

In Phase 1, the keyboard dose escalation design will govern the number of subjects to be enrolled. It is estimated 27 to 54 subjects may be enrolled, i.e., ~3-6 subjects for each of the 4 dose levels across both arms (monotherapy and combination therapy). Based on the cumulative data from subjects treated in the dose finding phase, the MTD or RP2D will be selected for further evaluation in the dose expansion portion of the study. Once identified, an

additional 3-6 subjects may be treated at the RP2D to confirm safety before proceeding to Phase 2.

In Phase 2, treatment with TAC01-HER2 will be evaluated both as a monotherapy (**Group A**), and in combination with pembrolizumab (**Group B**) in subjects with gastric and esophageal adenocarcinoma cancer using a Simon 3-stage design:

In Phase 2, up to 36 subjects will be enrolled in monotherapy **Group A** using a Simon 3 stage design assessing futility to show a maximum- ineffective ORR of 6.0% and a minimum effective ORR of 20%. If 0 subjects have a response among the first 11 subjects in the cohort, the study will be stopped for a lack of efficacy. If >0 subjects have a response, then another 14 subjects will be enrolled, for a total of 25 monotherapy subjects. If ≤2 of the 25 subjects have a response, the study will be stopped for lack of efficacy. If >2 subjects have a response, then another 11 subjects will be enrolled in the third stage, for a total of 36 monotherapy subjects. If ≤4 of the 36 subjects have a response, then treatment with TAC01-HER2 as a monotherapy will not be considered as having adequate efficacy to continue investigation in HER2+ subjects. If >4 of the 36 subjects have a response, then treatment with TAC01-HER2 as a monotherapy will be considered efficacious and continued clinical study investigations will be warranted. The assumed ORR was selected based on the results of the TAGS study for Trifluridine/tipiracil, which enrolled gastric cancer and GEJ AC subjects after 2 prior lines of therapy. Since the ORR in that study was 4% (Shitara 2018), it was considered that the assumed 20% ORRs for Group A is clinically meaningful.

In Phase 2, up to 34 subjects will be enrolled in combination therapy **Group B** using a Simon 3-stage design assessing futility to show a maximum ineffective ORR of 8.4% and a minimum effective ORR of 25%. If 0 subjects have a response among the first 9 subjects in the cohort, the study will be stopped for a lack of efficacy. If >0 subjects have a response, then another 10 subjects will be enrolled, for a total of 19 combination therapy subjects. If ≤2 of the 19 subjects have a response, the study will be stopped for lack of efficacy. If >2 subjects have a response then another 15 subjects will be enrolled in the third stage, for a total of 34 combination therapy subjects. If ≤5 of the 34 subjects have a response, then treatment with TAC01-HER2 in combination with pembrolizumab will not be considered as having adequate efficacy to continue investigation in HER2+ subjects. If >5 of the 34 subjects have a response, then treatment with TAC01-HER2 in combination with pembrolizumab will be considered efficacious and continued clinical study investigations will be warranted. The assumed clinically meaningful ORR for group B was also selected based on the results of the TAGS study for Trifluridine/tipiracil. Since the ORR in that study was 4% (Shitara 2018) and given the anticipated add on benefit for the combination it was considered that the assumed 25% ORRs for group B is clinically meaningful.

Simon Three-Stage Design Sample Size and Cutoff Requirements for Phase 2 (Dose Expansion)		
Parameter	Group A	Group B
Maximum non-effective rate	6.0%	8.4%
Minimum effective rate	20.0%	25.0%
First stage total N	11	9
First stage cutoff	0	0
Second stage total N	25	19
Second stage cutoff	2	2
Final stage total N	36	34
Final stage cutoff	4	5

For the efficacy analysis, the ITT population is defined as any subject that received at least 1 course of TAC01-HER2.

Subjects who are in DLT evaluation cohorts will be considered evaluable if they complete the defined DLT observation period. Estimates of ORR and other response proportions (e.g., DCR) will be presented together with 95% confidence intervals calculated using the Clopper-Pearson method. Kaplan-Meier estimations will be used for the analysis of time-to-event endpoints, including DOR, OS, PFS, or TTP.

The cellular kinetics of TAC01-HER2 will be determined from individual concentration-time profiles of circulating TAC T cells and characterized in peripheral blood and summarized by treatment arm.

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ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ACT	Adoptive T cell transfer
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the concentration-time curve
β-hCG	Beta human chorionic gonadotropin
BSA	Body surface area
BTC	Biliary tract cancer
CAP	College of American Pathologists
CAR	Chimeric antigen receptor
CBC	Complete blood count
CD	Cluster of differentiation
CD3ζ	CD3 zeta
CFR	Code of Federal Regulations
CI	Confidence interval
c/kg	Cells per kg
C_{last}	Last observed quantifiable level of transgene
CLIA	Clinical Laboratory Improvements Amendments
C_{max}	Maximum concentration (or peak cell expansion) after infusion
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTLA	Cytotoxic T-lymphocyte-associated protein

Abbreviation or Term	Definition/Explanation
CYC	Cyclophosphamide
D	De-escalate
DARPin	Design ankyrin repeat protein
DCR	Disease control rate
DIC	Disseminated intravascular coagulation
DILI	Drug induced liver injury
DLBCL	Diffuse large B cell lymphoma
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRESS	Drug Rash with Eosinophilia and Systemic Symptom
DSMC	Data Safety Monitoring Committee
E	Escalate
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EEG	Electroencephalogram
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EOS	End of study
ERBB2/erbB-2	Erythroblastic oncogene B
FBR	Future biomedical research
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridization
FNA	Fine needle aspiration
FT3	Free triiodothyronine
FT4	Free thyroxine
G-CSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
gDNA	Genomic DNA
GEJ	Gastroesophageal junction
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAMA	Human anti-mouse antibodies

Abbreviation or Term	Definition/Explanation
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
ID	Identification
IEC	Independent Ethics Committee
IFN-γ	Interferon γ
IgG/IgG4	Immunoglobulin G/G4
IgV	Immunoglobulin variable
IHC	Immunohistochemistry
IL	interleukin
IND	Investigational New Drug
INR	International normalized ratio
IO	Immuno-oncology
irAE	Immune-related adverse event
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous(ly)
KM	Kaplan-Meier
Lck	Lymphocyte-specific protein tyrosine kinase
LDC	Lymphodepletion chemotherapy
LDH	Lactate dehydrogenase
LTFU	Long-Term Follow-Up
LVEF	Left ventricular ejection fraction
mAB	Monoclonal antibody
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
MFI	Mean fluorescence intensity

Abbreviation or Term	Definition/Explanation
MHC	Major histocompatibility complex
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MUGA	Multigated acquisition (scan)
NCI	National Cancer Institute
NCI-N87	Human gastric epithelial cell line
NE	Non-evaluable
NGS	Next generation sequencing
NRG	NOD.Cg-Rag1tm1Mom Il2rgtm1Wjl/SzJ immuno-deficient mouse model
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
O_2	Oxygen
OE19	Oesophageal adenocarcinoma cell line
ORR	Objective response rate
OS	Overall survival
OVCAR-3	Human ovarian carcinoma cell line
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
Pembro	Pembrolizumab
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PKCϴ	Protein kinase C-theta
PO	By mouth
PR	Partial response
pRBC	Packed red blood cell
PT	Prothrombin time
PTT	Partial thromboplastin time
p_{target}	Target toxicity probability
Q	Every
qPCR	Quantitative polymerase chain reaction

Abbreviation or Term	Definition/Explanation
r/r	Relapsed/refractory
RCL	Replication-competent lentivirus
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
S	Stay
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
scFv	Single-chain variable antibody fragment
SCID	Severe combined immunodeficiency
SD	Stable disease
SDF-1	Stromal cell-derived factor 1
SJS	Stevens-Johnson Syndrome
SOC	Standard-of-care
SOE	Schedule of events
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
TAC	T cell antigen-coupler
TACΔ	TAC lacking an antigen binding domain
TCR	T cell receptor
TEAE	Treatment-emergent adverse event
TENS	Toxic epidermal necrolysis
T_{last}	Level of transgene at the last quantifiable time point
TLS	Tumor lysis syndrome
T_{max}	Time to reach C_{max}
TMDD	Target-mediated drug disposition
T_{reg}	Regulatory T cell
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
UPM	Unit probability mass
US	United States
W	Week
WHO-DD	World Health Organization Drug Dictionary
ZAP70	Zeta-chain-associated protein kinase

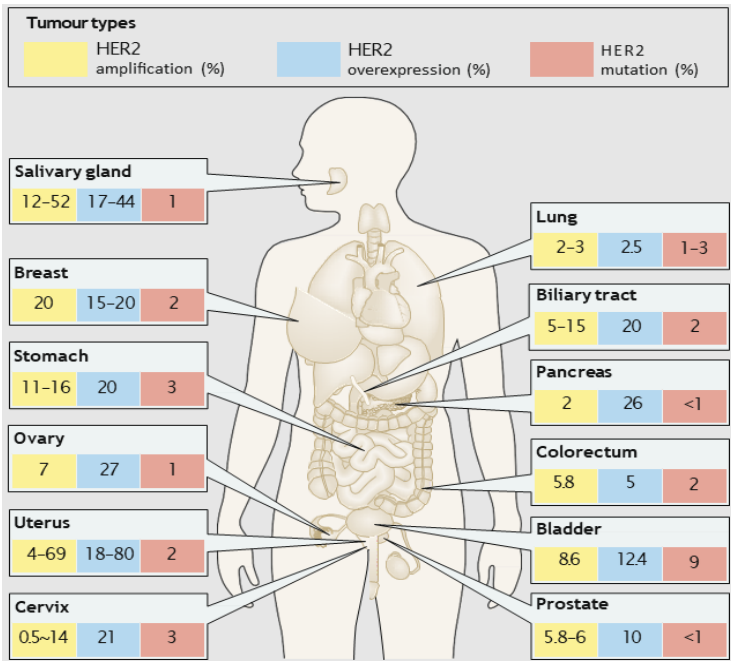
Abbreviation or Term	Definition/Explanation
λz	Apparent terminal elimination rate constant

1. INTRODUCTION AND STUDY RATIONALE

1.1. HER2-positive Solid Tumors

The activation of human epidermal growth factor receptor 2 (HER2) signaling observed in approximately 20% of breast cancers is the result of overexpression, owing to erythroblastic oncogene B (ERBB2; Oh 2020), also known as cluster of differentiation (CD) 340, amplification or activating somatic mutations (Yarden 2001). HER2 overexpression has been described in a variety of other solid tumors, including gastric and gastroesophageal junction (GEJ) cancers, biliary tract cancer (BTC), colorectal cancer (CRC), non-small-cell lung cancer (NSCLC) and bladder cancer, with incidences varying from >50% of uterine cancers to around 2% of NSCLCs (Figure 1). Genomic profiling of human cancers has revealed recurrent somatic mutations in ERBB2, typically occurring in the absence of amplifications (Chmielecki 2015, Schram 2017, Zehir 2017).

Figure 1: Frequency of HER2 Alterations Across Tumor Types



ERBB2 amplifications or mutations and HER2 overexpression have been detected in a wide range of different tumor types. Nonetheless, as suggested by the experience with gastric cancer, the presence of targetable alterations alone is not sufficient for a response to HER2-targeted therapies.

1.2. HER2 as a Therapeutic Target

Receptor tyrosine-protein kinase erbB-2, also known as HER2, is a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases. Heterodimerization of this receptor with other members of the EGFR family, typically owing to HER2 overexpression,

results in the autophosphorylation of tyrosine residues within the cytoplasmic domain of the heterodimer and initiates a variety of signaling pathways leading to cellular proliferation and tumorigenesis (Yarden 2001).

HER2 is an established therapeutic target in a large subset of women with breast cancer; a variety of agents including trastuzumab, pertuzumab, lapatinib, neratinib and ado-trastuzumab emtansine have been approved for the treatment of HER2-positive (HER2+) breast cancer. HER2 is also overexpressed in subsets of patients with other solid tumors. Notably, the addition of trastuzumab to first-line chemotherapy has improved the overall survival (OS) of patients with HER2+ gastric cancer and has become the standard-of-care treatment for this group of patients. However, studies involving pertuzumab, lapatinib and ado-trastuzumab emtansine have failed to provide significant improvements in the outcomes of patients with HER2+ gastric cancer.

HER2-targeted therapies are also being tested in patients with other solid tumors harboring HER2 overexpression, and/or amplifications or other mutations of the gene encoding HER2, including BTC, CRC, NSCLC, and bladder cancer. The experience with gastric cancer suggests the successes observed in HER2+ breast cancer might not be replicated in these other tumor types, owing to differences in the level of HER2 overexpression and other aspects of disease biology.

1.3. Adoptive T Cell Therapy

Adoptive T cell transfer (ACT) using autologous T cells genetically engineered to express chimeric receptors is a promising approach to treat cancer (June 2018, Miliotou 2018). The introduction of a chimeric receptor into a patient's T cells re-directs a patient's own immune cells to tumor cells and provides mechanisms that lead to T cell activation and, consequently, tumor cell killing. Molecularly, this is achieved by the chimeric receptor via an extracellular antigen-specific binding domain, that mediates tumor cell recognition, and – in the case of chimeric antigen receptors (CARs) – an intracellular transactivation domain that induces T cell activation upon binding to the antigen.

Effective clinical applications of such T cell therapies are frequently hampered by serious and potentially fatal adverse events (AEs). These include cytokine release syndrome (CRS), macrophage activation syndrome (MAS), hemophagocytic lymphohistiocytosis (HLH), and immune effector cell-associated neurotoxicity syndrome (ICANS; Barrett 2014, Maude 2016, Maude 2014a). In addition, insufficient in vivo T cell expansion and persistence, as well as premature T cell exhaustion as a result of tonic signaling may reduce the potency of the T cell product (Long 2015). Several of these features are likely a direct consequence of the specific design of the CAR protein and, particularly, attributed to its own signaling domain which activates T cells directly and without the endogenous T cell receptor (TCR).

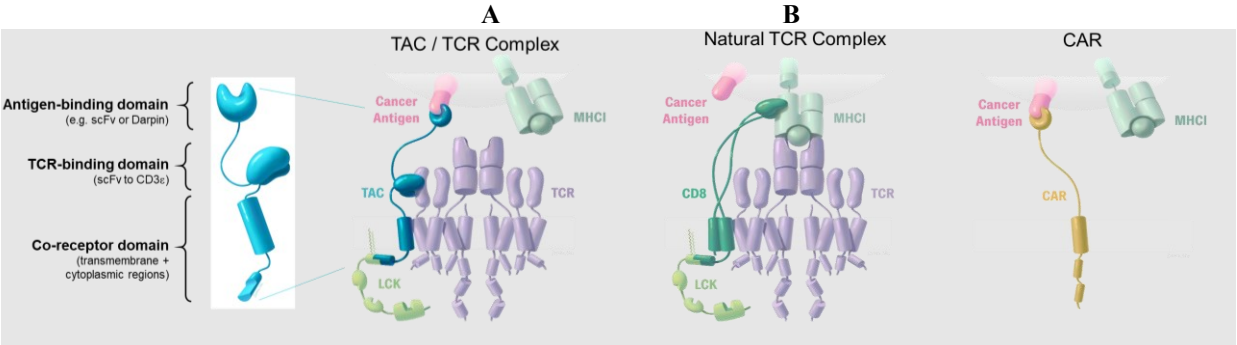
1.4. T Cell Antigen-Coupler Technology

The manufacturing aspects of the T cell antigen-coupler (TAC) T cell therapy are similar to those of other engineered T cell products which involve an extraction of T cells from the subject, followed by the genetic engineering with a chimeric receptor using retro-/lenti-viral transduction,

expansion of engineered T cells ex vivo, and lastly, re-administration of engineered T cells to the subject.

TAC T cells are T cells genetically engineered via lentiviral insertion of the HER2-directed TAC transgene which encodes a chimeric, partially humanized receptor that was designed to exert 2 key functions: first, to redirect a T cell to tumor cells via the specific recognition of a tumor associated antigen expressed on the surface of tumor cells, and second, to activate that same T cell via recruitment of the TCR complex and its natural, downstream intracellular signaling pathways (Figure 2). Thus, TAC is expected to induce antitumor responses via a mechanism that mimics T cell activation under physiologic conditions (Helsen 2018). This mechanism contrasts with conventional chimeric receptors, such as CARs, that activate T cells independently of the endogenous TCR via their own intracellular signaling domain.

Figure 2: TAC T Cell Receptor versus CARs and the Natural TCR Complex



(A) Outline of the 3 major protein domains in the chimeric TAC receptor. **(B)** Comparison of the molecular mechanisms that control T cell activation in TAC-expressing T cells (left), normal cells (middle), and T cells engineered with CARs (right). **Left**: The TAC receptor (cyan) re-directs the TCR-CD3 complex towards an antigen of choice. A single-chain variable antibody fragment (scFv) is used to recruit the TCR-CD3 complex. Co-receptor properties are incorporated by including the CD4 hinge, transmembrane region, and cytosolic tail (green). **Middle**: Naturally occurring TCR-CD3 complex (purple) interacts directly with the cancer antigen presented by the Major Histocompatibility Complex (MHC). Meanwhile, the CD8/CD4 co-receptor (CD8 shown in dark green) interacts with MHC I/II in an antigen-independent manner. Together, these interactions comprise the first step in T cell activation. **Right**: The CAR receptor (yellow) binds to a cancer antigen of choice and activates T cells independently of the TCR-CD3 complex by its own intracellular transactivation domain.

The various functions of the TAC receptor are carried out by 3 main structural domains (Figure 2):

1. Antigen-binding domain: Antigen recognition is mediated by the N-terminal extracellular antigen-binding domain, such as a HER2-targeted designed ankyrin repeat protein (DARPin). In the absence of antigen, there are no signs of auto-activation or tonic signaling (Helsen 2018).

2. TCR-recruitment domain: A central and extracellular protein domain (CD3ε-targeting scFv) facilitates the interaction of TAC with the TCR/CD3 complex. This CD3-binding domain is critically necessary for TAC activation. TAC constructs lacking this domain do not show activity (Helsen 2018).

3. Co-receptor domain: The C-terminal co-receptor domain consists of an extracellular hinge domain, as well as the transmembrane and cytoplasmic domains derived from the natural CD4 co-receptor, anchoring the TAC receptor into the cellular membrane. The cytoplasmic tail includes the lymphocyte-specific protein tyrosine kinase (Lck) binding site of CD4 which is expected to contribute to T cell activation upon recruitment of the TCR. In the absence of the cytoplasmic tail, surface expression of the TAC is greatly reduced, and T cell activation is impaired (unpublished data).

1.5. TAC01-HER2 Investigational Product

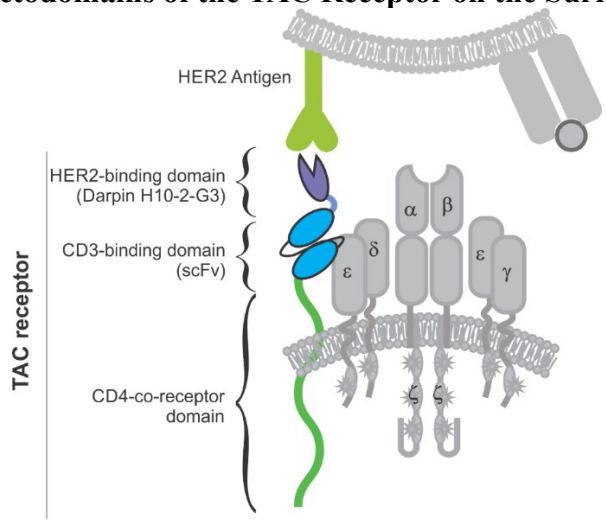
1.5.1. Product Name and Description

TAC01-HER2 is an autologous T cell product comprising T cells expressing a HER2-specific TAC, a chimeric receptor that is genetically engineered into T cells via lentiviral transduction to furnish T cells with 2 main functions: (i) redirection to and specific recognition of HER2+ cells, and (ii) T cell activation via the endogenous TCR.

1.5.2. Structure

The chimeric TAC-HER2 receptor consists of 3 main functional domains: (Figure 3): (i) an extracellular HER2-binding domain provided by the H10-2-G3 designed ankyrin repeat protein (DARPin); (ii) an extracellular TCR/CD3ε-binding domain (huUCHT1 scFv); and (iii) a membrane-anchoring domain that consists of the transmembrane and cytoplasmic domains of CD4. The HER2-binding domain is designed to bind to the HER2 surface antigen expressed on HER2+ cells, including HER2+ non-malignant cells. The TCR/CD3ε binding domain is designed to recruit the endogenous TCR complex. The cytoplasmic tail includes the Lck binding site of CD4 which is expected to contribute to T cell activation upon recruitment of the TCR.

Figure 3: Endo and Ectodomains of the TAC Receptor on the Surface of TAC T Cells



The TAC receptor re-directs the TCR-CD3 complex (grey: α, β, γ, δ, ε, ζ chains) towards the HER2 antigen. The 3 major TAC protein domains are shown. Purple: HER2-directed DARPin (H10-2-G3), blue: CD3-binding (scFv), dark green: CD4 co-receptor (membrane anchoring).

1.5.3. Dosage Form

The TAC01-HER2 product is a suspension of genetically modified autologous T cells expressing the HER2-TAC receptor for infusion (i.e., HER2-targeted TAC T cells) containing 10% dimethyl sulfoxide (DMSO) in approximately 20 mL.

1.5.4. Administration

TAC01-HER2 will be administered as an intravenous (IV) infusion approximately 72 hours after completion of lymphodepleting chemotherapy (LDC). LDC will preferentially consist of 3 consecutive days of fludarabine (30 mg/m^2 IV) or clofarabine (52 mg/m^2 IV) and cyclophosphamide (300 mg/m^2 IV) with or without mesna IV. Central venous access is recommended for the infusion of TAC01-HER2.

If fludarabine or clofarabine is unavailable (due to national shortages), subjects can be treated with 3 consecutive days of cyclophosphamide (300 mg/m^2 IV) with or without mesna IV or with bendamustine 90 mg/m^2 daily for 2 days for subjects who cannot tolerate cyclophosphamide.

The dose intensity of either the primary (fludarabine or clofarabine + cyclophosphamide) or backup (cyclophosphamide or bendamustine) regimens can be modified based on a subject's complete blood count (CBC) and creatinine clearance, upon discussion with the Medical Monitor.

1.6. Pembrolizumab

1.6.1. Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death protein 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on nonclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable nonclinical safety profile and is in clinical development as an 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 Investigator's Brochure (IB).

Refer to the IB/approved labeling for detailed background information on MK-3475.

1.6.2. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T_{reg}) 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 (Dudley 2005, Hunder 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin 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 (PD-L1 and/or PD-L2; Greenwald 2005, Okazaki 2001).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki 2001, Chemnitz 2004, Sheppard 2004, Riley 2009). 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 (Parry 2005 , Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in breast, lung, pancreatic, colorectal, gastric, endometrial, ovarian, and other solid tumor types.

1.6.3. Nonclinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking the 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 (Hirano 2005, Blank 2004, Weber 2010, Strome 2003, Spranger 2014, Curran 2010, Pilon-Thomas 2010). 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 CRC (Strome 2003, Curran 2010, Pilon-Thomas 2010, Nomi 2007, Zhang 2004). In such studies, tumor infiltration by CD8+ T cells and increased interferon γ (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 (Curran 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

1.6.4. Justification for Dose

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5- to 7.5-fold exposure range (refer to the IB)

- Population pharmacokinetic (PK) analysis showing that both fixed-dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from 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 2262 participants were enrolled with melanoma and 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 these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant 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.

1.6.5. Timing of Pembrolizumab Administration

Pembrolizumab 200 mg IV will be administered Q3W starting on Day 21 or Day 14 from administration of TAC T cells. The initial combination dose-escalation cohort will have pembrolizumab administered on Day 21. For all remaining cohorts, pembrolizumab will be administered on Day 14 if no dose-limiting toxicities (DLTs) or safety issues are identified (as approved by the Data Safety Monitoring Committee [DSMC]). The Day 14 time point was chosen based on nonclinical in vivo data showing maximal TAC T cell expansion in the tumor around and after Day 7 post IV administration. The Day 21 time point for the initial pembrolizumab administration in the combination arm was chosen as an additional safety precaution to allow an extra week for any TAC T cell-related AEs to emerge and be managed, as appropriate.

Dose modifications and discontinuations will follow the guidelines described in Appendix H and Appendix I. The recommended dosage modifications based on adverse reactions can also be found in Table 9.

1.7. Study Rationale

Despite recent therapeutic developments for patients with advanced, metastatic, unresectable HER2-positive (HER2+) solid tumors, a significant unmet medical need still exists, especially in solid tumors where there are no approved HER2-targeted therapies and/or in tumors with low or intermediate HER2 expression. The TAC technology is a novel approach to modifying a patient's own T cells, herein referred to as TAC T cells, and using them in the treatment of solid tumors. TAC T cells are produced through genetic engineering, incorporating TAC receptors into a patient's own T cells. This redirects these enhanced T cells to specific cancer antigens and, upon recognition, activates them by co-opting the natural signaling pathways of the endogenous TCR.

In the TAC01-HER2 product, TAC T cells use the HER2 antigen, which is present on the surface of cancer cells, to recognize and eradicate tumor cells. Promising outcomes have been observed in mouse models, with TAC T cells accumulating within solid tumors, resulting in a robust antitumor efficacy profile paired with a favorable safety profile. TAC T cells can also persist for extended periods of time in mice and protect the host from tumor regrowth. Consequently, it is hypothesized TAC01-HER2 monotherapy will be safe and effective in treating patients with HER2+ solid tumors and can provide a significant therapeutic benefit in an area of high unmet medical need.

Phase 1 will evaluate escalating single doses of TAC01-HER2 (on Day 1) as a monotherapy, and in combination with a fixed approved prescription pembrolizumab dose (200 mg Q3W) beginning on either Day 21 or Day 14 to identify the recommended Phase 2 doses (RP2Ds) for TAC01-HER2 treatment in subjects with HER2+ solid tumors, who have progressed after 2 prior lines of therapy.

In vitro nonclinical studies conducted by Triumvira suggest that TAC T cells specifically engage with HER2+ cancer cells. As part of this T cell activation process, TAC T cells, similar to any other activated T cell, can induce the expression of PD-1 and PD-L1, which can consequently lead to reduced TAC T cell activity. Blocking PD-1 signaling via an anti-PD-1 checkpoint blockade, such as pembrolizumab, can counteract this inhibitory function. Therefore, these observations highlight the importance of evaluating the combination of TAC01-HER2 treatment with PD-1 blockade to potentially enhance the antitumor activity of administered TAC T cells. Attenuating the eventual exhaustion of TAC T cells may also facilitate the recruitment of endogenous polyclonal immune cells to overcome tumor heterogeneity and to prevent antigen escape (Grosser 2019). Mechanistically, this occurs through first treatment with TAC01-HER2, followed by pembrolizumab to block PDL1 and PD-L2 ligands on cancer cells from binding to PD-1 receptors on the resultant circulating TAC T cells.

In addition to 3+ HER2 tumors, subjects with low-HER2 expressing solid tumors (i.e., 2+ and 1+) will also be allowed to participate in this trial. These subjects constitute an area of high unmet medical need, e.g., 60% of all breast cancer patients have low-HER2 expressing tumors (Modi 2022). Nonclinical studies have demonstrated that TAC T cells are equally effective in eliciting antitumor activity regardless of HER2 expression levels (Figure 7) and are active in killing tumor cells that are resistant to trastuzumab and pertuzumab. In addition, trastuzumab deruxtecan, a HER2-targeting antibody drug conjugate, has recently demonstrated significant success in treating low HER2-expressing tumors in breast cancer patients (i.e., with an objective response rate [ORR] of 37.0% in a Phase 1B trial [Modi 2020] and 52.3% in the Destiny Breast04 Phase 3 trial [Modi 2022]), with a median duration of response (DOR) of 10.7 versus 6.8 months (in the Phase 3 trial) for trastuzumab deruxtecan treatment vs the physician's choice of chemotherapy (Modi 2022).

In conclusion, HER2 overexpression and/or amplification is observed in breast, gastric, lung, pancreatic, salivary, vaginal, endometrial, gall bladder, colorectal, and cervical cancers. It activates numerous oncogenic signaling pathways (e.g., PI3K/AKT and Ras/Raf/ERK) resulting in improved malignant cell survival, proliferation, migration, and resistance to immunotherapy (Vafaei 2022). HER2-targeted therapies continue to evolve in treating patients with varying levels of HER2 expression. However, continued advances using novel targeted therapies are still needed to treat patients more effectively and with fewer side-effects.

1.8. TAC01-HER2 Monotherapy Rationale

In vitro and in vivo pharmacology studies have characterized the mechanism of action, dose response relationships, efficacy, PK, biodistribution, improved safety parameters, and the potential influence on TAC01-HER2 bioactivity produced from multiple healthy donors of TAC

T cells, as compared with CAR-T cells. These nonclinical studies were carried out using a panel of cancer cell lines representative of human HER2+ malignancies, which included ovarian cancer (OVCAR-3), gastric cancer (NCI-N87) and gastroesophageal cancer (OE19). Cancer cells were either co-cultured transiently with TAC T cells in vitro or grown as subcutaneous tumor xenografts in immunodeficient NRG mice before TAC01-HER2 administration. The data demonstrate TAC T cells reproducibly lead to elimination of HER2+ tumor cells in vitro and in vivo. During these nonclinical studies, no treatment-related changes were observed in mobility, grooming, and overall constitution. In addition, a pivotal 60-day pharmacology/safety study was conducted in immunodeficient NRG mice carrying established OE19 tumor xenografts and did not reveal any TAC-related toxicities. The study observed the effects of TAC01-HER2 given as an IV tail vein injection at a therapeutic dose level (3 x 10^8 TAC T cells/kg) and at the maximally feasible dose level (6 x 10^8 TAC T cells/kg). The study observed tumor burden, survival, T cell expansion, serum cytokines, clinical chemistries, and histopathology of vital organs. Dose conversions from mouse to humans show that the therapeutic dose used in mice (3 x 10^8 TAC T cells/kg) was at least 3-times higher than the lowest dose in the proposed clinical study, and the highest dose levels used in mice (6 x 10^8 TAC T cells/kg) was at least 6-times greater (based on body surface area [BSA]) than the highest dose levels in the proposed clinical study. However, data produced in animal models should be interpreted with caution and are considered supportive information given the marked differences of TAC T cell host- interactions in these models compared with humans. See the IB for additional information.

Dose levels used in nonclinical pharmacology studies in mice were determined empirically and typically ranged from 2.5 x 10^7 to 6 x 10^8 TAC T cells per kg (c/kg), assuming a mouse body weight of 20 g for various TAC01-HER2 products. The maximum feasible dose (MFD) was typically 3-fold higher (e.g., 6 x 10^8 c/kg). Human equivalent dose levels were calculated based on a direct c/kg conversion and separately on body surface area. These calculations indicated the proposed clinical monotherapy starting dose (i.e., Dose Level 1) was approximately 2-3 logs lower than dose levels used in mice.

However, similar to other forms of cellular immune therapy, dose levels investigated in mice do not accurately predict dose levels in humans for several reasons (CAR T cell Products Draft Guidance 2022). Therefore, additional information was considered to estimate the starting dose in humans, such as, dose levels of YESCARTA® and KYMRIAH®, which were both safe and biologically active in studies in humans.

In Group A of Phase 2, a second TAC01-HER2 dose may be administered ≥4 weeks after the first dose if the subject has tolerated the first TAC01-HER2 infusion and if additional inclusion/exclusion criteria are met (Section 4.3). Modeling multidosing in mice was considered; however, was not done as it cannot inform on dose regimens in humans. Thus, the most appropriate animal model for studying the nonclinical pharmacology and safety of TAC01-HER2 are immunodeficient mice (NRG/NSG) carrying human, HER2-expressing tumor xenografts. However, these mice have deficient immune systems that do not recapitulate the complex immune system in humans and therefore present critical limitations in extrapolating mouse data to humans as follows:

- Nonclinical modeling of safety: A chief parameter for defining the timing of the second TAC01-HER2 dose is safety of the first infusion. However, immunocompromised mice do not represent an adequate model to assess immune-related toxicities and, therefore, lack the ability to observe a comprehensive spectrum of immune related toxicities relevant to humans.
- Nonclinical modeling of PK: Multidose regimens are often guided by PK parameters seen in nonclinical models. However, PK of cell therapies is highly influenced by clearance mechanisms that are driven by the host immune system and for instance cause graft rejection. Immunodeficient mice do not provide the appropriate host background that will influence PK in humans and therefore are not appropriate models to evaluate multidose regimens. Furthermore, the PK profile of transferred T cells may be influenced by T cell trafficking to the tumor and in vivo T cell expansion, both of which cannot be anticipated in nonclinical models.
- Immunocompromised mouse models are susceptible to graft versus host disease, which can confound efficacy and safety assessments of cell therapies.

In the proposed clinical study, the second dose will be administered at least 4 weeks after the first dose. Therefore, the rationale for a single dose nonclinical study to support administering the second TAC01-HER2 dose in humans is in accordance with the ICH S9 guidance, which state a single dose nonclinical study supports a clinical schedule of once every 3-4 weeks (Nonclinical Evaluation for Anticancer Pharmaceuticals). Since nonclinical models are of limited value for cell therapies, additional information available from other cell therapies in clinical development for solid tumors were considered, such as 1 subject was safely administered a second TAC01-HER2 dose under IND 27239 and multiple clinical studies allowed administration of a second dose of CAR-T cells for the treatment of solid tumors. This additional information supports the rationale that administration of a second dose at least 28 days after the first dose would be expected to be safe for evaluation in a Phase 2 clinical study.

1.9. Anti-PD-1 Combination Therapy Rationale

1.9.1. Background

PD-1, also known as CD279, is an immune checkpoint and surface receptor expressed on T cells and other immune cells that promotes self-tolerance and guards against autoimmunity. In T cells, it is upregulated after TCR-mediated T cell activation and functions in a negative feedback loop to inhibit T cell activity. The PD-1 inhibitory function requires interacting with its respective ligands, PD-L1 or PD-L2, expressed by normal cells including other T cells, often during an immune response to dampen it.

PD-1 ligands, specifically PD-L1, are also frequently expressed on tumor cells to escape immune surveillance. Therefore, anti-PD-1 strategies, such as the anti-PD-1 mAb pembrolizumab, have successfully led to the reinvigoration of exhausted T cells and T cell-mediated antitumor responses. Tumors associated with improved clinical responses to checkpoint blockade are those with known high PD-L1 expression; however, responses can also be observed in tumors without PD-L1 expression (Garon 2015; Topalian 2012). In these tumor cells, PD-L1 expression is

believed to be induced by cytokines, such as IFN-γ and TNF-α which are secreted by T cells that have infiltrated the tumor bed, particularly after checkpoint blockade (Spranger 2013; Tumeh 2014; Herbst 2014). Since TAC T cell activation can also impact the PD1/PD-L1 signaling axis (Section 1.9.2.1), this study will not mandate subjects have prerequisite PD-L1 tumor expression levels to be enrolled; however, PD-L1 levels will be determined at Screening/Baseline, or after enrollment using local laboratory results if necessary.

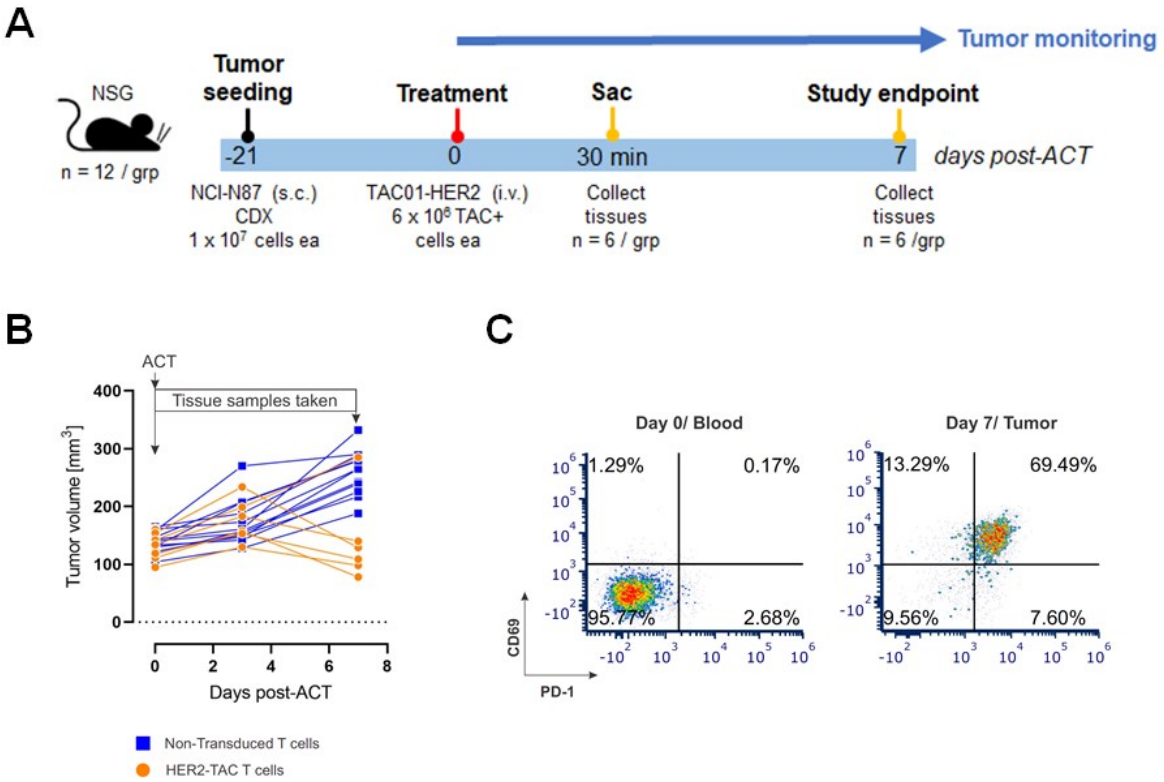
1.9.2. Nonclinical Studies

1.9.2.1. Nonclinical Rationale for Combining TAC01-HER2 with Pembrolizumab

To assess the relevance of PD-1/PD-L1 signaling in TAC T cells, Triumvira conducted a series of nonclinical experiments evaluating the expression of these markers in scenarios of ongoing tumor cell killing. Collectively, these data show PD-1 and PD-L1 are specifically induced during TAC T cell-mediated antitumor responses and suggest that a prolonged expression of these markers can reduce the antitumor activity of TAC T cells. Accordingly, studies using isogenic cancer cells, which differ in PD-L1 expression levels, demonstrated that high PD-L1 levels expressed on tumor cells can limit TAC T cell activity which, in turn, can be restored by adding pembrolizumab. Relevant experiments are described as follows.

In 1 example, PD-1 expression on T cells was evaluated in the HER2+ N87 gastric cancer mouse model. Mice with established human tumor xenografts were treated with TAC01-HER2, derived from a healthy donor, and TAC T cells were extracted 30 minutes and 7 days after dosing from blood and tumor tissue, respectively (Figure 4A). The Day 7 time point was chosen because it reflected a time point during tumor regression that is ideal for the observation of T cells that drive the antitumor response (Figure 4B). Isolated T cells were subjected to flow cytometry analysis to assess the status of T cells by determining CD69 (activation) and PD-1 (exhaustion). In agreement with the TAC T cell profile after manufacturing, the data show that TAC T cells lack expression of either marker at the Day 0 time point (blood) and indicate that these T cells have not yet encountered any HER2 antigen (Figure 4C). In contrast, TAC T cells recovered from HER2+ tumors on Day 7 had elevated expressions of CD69 and PD-1, indicative of specific T cell activation. If PD-1 expressed over an extended period of time, leads to T cell exhaustion, then blocking PD-1 signaling may effectively interfere with T cell exhaustion and increase the potency of TAC T cells.

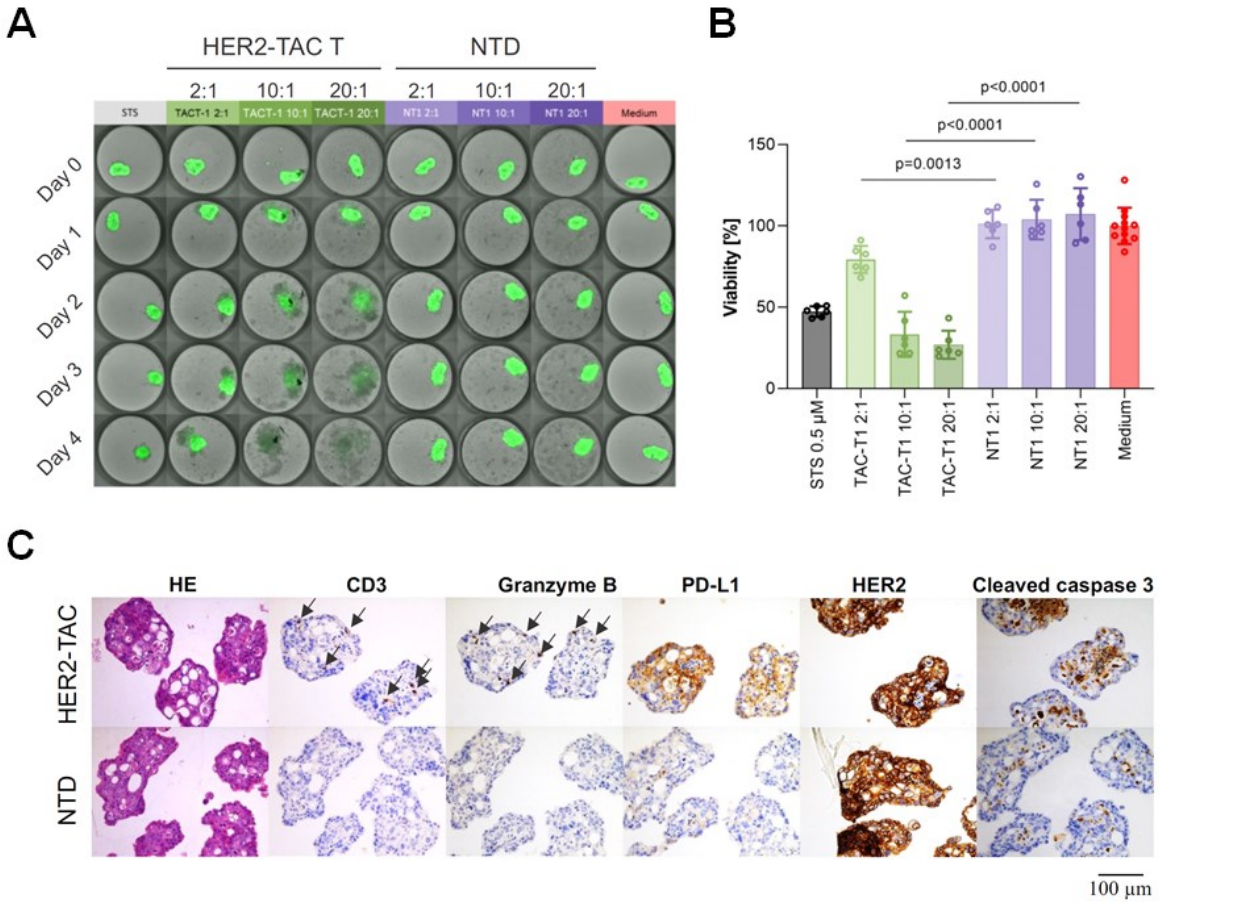
Figure 4: In Vivo Upregulation of PD-1 Levels in Activated TAC T Cells



(**A**) Study Design. NSG mice carrying established, subcutaneous human N87 gastric cancer xenografts were given a single IV bolus of 6 x 10^6 TAC+ HER2-TAC T cells (TAC01-HER2, Day 0). An equivalent number of non-transduced T cells was given to a separate group of animals as negative controls. Blood and tumor tissue was collected 30 minutes and 7 days after treatment for further analysis. (**B**) Tumor volumes of mice treated with TAC01-HER2 (orange) and non-transduced T cells (blue). (**C**) Flow cytometry analysis of PD-1 and CD69 in T cells derived from blood (Day 0) and tumor (Day 7).

In another example, PD-L1 expression was determined in HER2+ N87 tumor spheroids co-cultured with TAC01-HER2 for 4 days. While most spheroids were destroyed by the addition of TAC T cells (Figure 5A, B), some of the remaining spheroids (those exposed to lower number of TAC T cells) were formalin-fixed and paraffin-embedded, cut and used in immunohistochemistry (IHC) assays to investigate the antitumor mechanism of TAC T cells (Figure 5C). This analysis confirmed the migration of TAC T cells into spheroids, release of granzymes, and induction of apoptosis of tumor cells, according to the previously established mechanism of TAC T cell-mediated tumor killing. However, this analysis also revealed the specific induction of PD-L1 in these spheroids which is likely a consequence of TAC T cell activation and IFNγ secretion. Hence, both PD-1 and PD-L1 are induced upon TAC T cell mediated- antitumor responses, which if not countered by anti-PD-1 blockade, may lead to TAC T cell exhaustion.

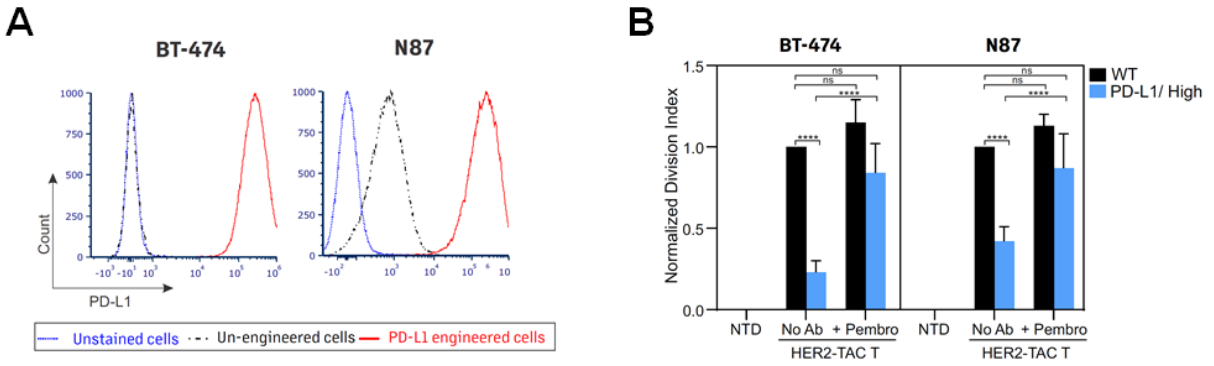
Figure 5: In Vitro Upregulation of PD-L1 Levels in HER2+ Tumor Spheroids Upon Binding and Subsequent Eradication with TAC T Cells



(**A**) Image of GFP-expressing N87 tumor spheroids (green) on Day 4 in co-culture with TAC T cells at various E:T ratios. Co-cultures with non-transduced T cells (NTD) served as controls. A loss of GFP fluorescence indicated the complete destruction of spheroids. Additional controls included spheroids cultured without T cells (medium) or with the apoptotic agent staurosporine (STS). (**B**) Quantification of viable N87 spheroids on Day 4. (**C**) IHC analysis of viable tumor spheroids harvested on Day 4 taken from wells with the lowest number of TAC T cells (E:T=2:1).

To directly assess the effects of PD-L1 and anti-PD-1 blockade on TAC T cells, isogenic cancer cells that exhibit either low or high levels of PD-L1 were co-cultured with TAC T cells in the presence or absence of pembrolizumab (Figure 6). The results indicated that PD-L1 quenched the ability of TAC T cells to proliferate, which was restored by the addition of pembrolizumab (Figure 6B).

Figure 6: Loss of TAC T Cell Activity Induced by high PD-L1 Levels on Tumor Cells Reversed by Pembrolizumab Addition



(**A**) PD-L1 surface expression in isogenic BT-474 breast cancer and N87 gastric cancer cell lines as determined by flow cytometry (parental cells: dotted black; PD-L1 engineered cells: solid red). X axis reflects the median fluorescence intensity. (**B**) Proliferation of T cells co-cultured with isogenic cancer cells in the presence or absence of pembrolizumab (60 µg/mL). Data were normalized to those of non-transduced T cell co-cultures and presented as division indices.

Summary:

In vitro nonclinical studies suggest that TAC T cells specifically engage with HER2+ cancer cells and can induce expression of PD-1 and PD-L1, which can consequently lead to reduced TAC T cell activity. Blocking PD-1 signaling using an anti-PD-1 checkpoint blockade, such as pembrolizumab, can counteract this inhibitory function. Therefore, these observations highlight the importance of combining TAC T cell therapy with a PD-1 blockade to potentially enhance the antitumor activity of administered TAC T cells. Attenuating the eventual exhaustion of TAC T cells may also facilitate the recruitment of endogenous polyclonal immune cells to overcome tumor heterogeneity and to prevent antigen escape (Grosser 2019).

1.9.2.2. TAC T Cell Activity Across Multiple HER-2 Expressing Cancer Cell Lines

Previous studies demonstrated that TAC-engineered cells are not reactive towards antigen-negative cells and that TAC lacking an antigen binding domain (ΔTAC) is unable to activate T cells (Helsen 2018). To investigate a HER2-dependent activation of TAC01-HER2 cells by cancer cells, TAC01-HER2 was cultured in the presence of various HER2-expressing cancer cells derived from a diverse set of human cancer types that includes breast (BT474, SKBR-3, HCC1954), ovarian (SK-OV-3), skin (LOX-IMVI), pancreatic (PANC-1), gastric (NCI-N87), and gastroesophageal cancer (OE19) (Table 1) (Lieber 1975; Fogh 1977; Lasfargues 1978; Park 1990; Lewis 1993; Rockett 1997; Fodstad 1998; Gazdar 1998; Chakrabarty 2013; Walsh 2013; Deguchi 2017; Ikediobi 2006). HER2 surface expression was determined by flow cytometry and normalized to the mean fluorescence intensity (MFI) observed in SKOV-3 cells, an ovarian cancer cell line with high HER2 expression. This data showed that HER2 expression varied substantially among cancer cell models and included PANC-1 derived from an epithelial cell carcinoma of the pancreas that presented very low HER2 expression which was only ~2-fold higher compared to other human non-malignant cells (Table 1).

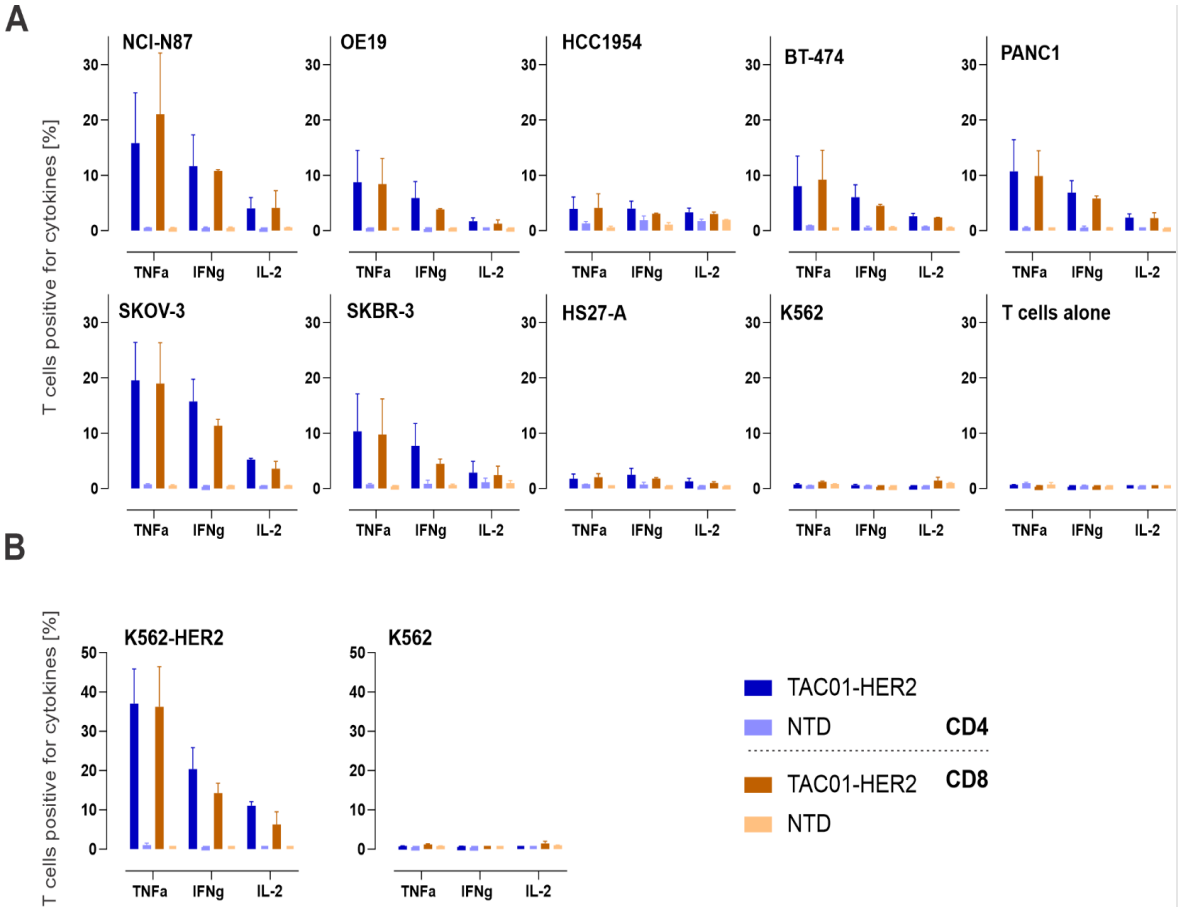
Table 1: HER2 Surface Expressions in Various Cancer Cell Lines

Cell Lines/Non-malignant Cells			Normalized HER2 Expression
Cancer Cells			
SKOV-3	Ovary	Adenocarcinoma	1.000
SKBR-3	Breast	Carcinoma	1.000
BT-474	Breast	Ductal carcinoma	0.916
HCC1954	Breast	Epithelial cell carcinoma	0.756
OE19	Esophagus	Carcinoma	0.409
PANC-1	Pancreas	Epithelial cell carcinoma	0.036
Non-malignant Cells			
AoSMC	Aorta/Heart	Smooth muscle cells	0.019
CCD-19	Lung	Fibroblasts	0.012
HCM	Heart	Cardiomyocytes	0.021
HS-27A	Bone marrow	Stromal cells	0.020

For assessing T cell activation, TAC01-HER2 was co-cultured with target cells for 4 days and analyzed via flow cytometry for their ability to produce cytokines. As negative controls, T cells alone (not exposed to tumor cells) and TAC01-HER2 co-cultured with HER2-negative K562 cancer cells were used. K562 cells are myelogenous leukemia cells and were chosen because HER2 is commonly expressed in cells of epithelial origin. In addition, an isogenic K562 cell line overexpressing HER2, Figure 7B, was created to test the requirement of HER2 during TAC01-HER2 activation. Cells derived from human bone marrow (HS-27A) endogenously expressing low levels of HER2 were included as a non-malignant reference. Activation of TAC01-HER2 cells was evaluated by measuring intracellular levels of TNFα, IFNγ and IL-2 cytokines.

The data revealed that TAC01-HER2 activity was minimal when exposed to the non-malignant HS-27A cells and was completely absent when exposed to HER2-negative K562 cells. In contrast, TAC01-HER2 was selectively activated when co-cultured with HER2 expressing K562 cells, demonstrating that TAC01-HER2 activation is strictly dependent on the HER2 antigen (Figure 7B). TAC01-HER2 was active against all HER2 positive malignant cells (Figure 7A); however, the extent of cytokine production varied across different co-cultures. Strikingly, TAC01-HER2 was strongly activated by PANC1 cancer cells despite the fact that it expressed relatively low levels of HER2.

Figure 7: In Vitro Activation of TAC T Cells Across Various Levels of HER2-Expressing Cancer Cell Lines



(**A**) TAC T cells or NTD cells were co-cultured with various cell lines for 4 hours in a 1:1 E:T ratio. (**B**) TAC T cells or NTD cells were co-cultured with K562 (HER2 negative) or K562 overexpressing HER2. Data shown represent the percentage of cells positive for indicated cytokines. In A and B, the mean of 2 different donors with error bars indicating the SEM are shown.

In conclusion, the activity observed in this co-culture was comparable to other cancer cells expressing very high levels of HER2, such as SKBR1 and OE19, supporting the rationale for using TAC01-HER2 in the treatment of cancers exhibiting both high and low HER2 expression levels.

CAR T Cell Studies:

Similar results were reported with CAR T cells in nonclinical mouse models. For example, Adusumilli et al. found that tumor cells upregulated PD-L1 expression levels in response to CAR T cell-secreted cytokines, with PD-1 expression levels on CAR T cells also becoming upregulated (Adusumilli 2021). To overcome this tumor-mediated adaptive resistance, Adusumilli et al. added pembrolizumab following CAR T cell administration. Results indicated

that exhausted CAR T cells were rescued by pembrolizumab, yielding enhanced efficacy and longer persistence of the CAR T cells (Adusumilli 2021; Supplementary Materials: Section 3.2.6).

1.9.3. Clinical Studies (Literature)

The safety and clinical activity of adding pembrolizumab to HER2-targeted therapies has recently been demonstrated with trastuzumab in metastatic esophagogastric cancer (O'Donnell 2019), and margetuximab in gastroesophageal adenocarcinoma (Catenacci 2020). Pembrolizumab was also combined with CD19-directed CAR T cell therapy in B cell lymphomas (Chong 2022) and to mesothelin-targeted CAR T cell therapy in metastatic lung and breast cancers, and malignant pleural mesothelioma (MPM; Adusumilli 2021).

A review of a Phase 1 clinical study using the mesothelin-targeted CAR T cell + pembrolizumab combination (Adusumilli 2021) suggests that TAC T cells can be used in combination with pembrolizumab to yield safe and more effective outcomes in subjects with solid tumors. In the mesothelin study, 27 total patients were treated with CAR T cells: 25 had MPM, and 1 each had metastatic lung and metastatic breast cancers. Eight monotherapy dose escalation cohorts consisted of 3 patients each (unless otherwise noted): 1.3×10^5, 2.3×10^5, 3.1×10^6, 4.3×10^6, 5.6×10^6, 6.1×10^7 (6 patients), 7.3×10^7, and 8.6×10^7 cells/kg. All patients, except the first 3, received a single dose of cyclophosphamide preconditioning (1500 mg/m^2). From these 24 cyclophosphamide + CAR T cell-treated patients, 23 had MPM, 18 of whom were treated with pembrolizumab 200 mg Q3W for a minimum 3 doses, with ≥3 months of follow-up after the third dose. The other 5 MPM patients did not receive pembrolizumab treatment and remained in the CAR T cell monotherapy group (i.e., cyclophosphamide + CAR T cell), with 1 breast cancer patient also not receiving pembrolizumab treatment.

The most frequently occurring treatment-emergent adverse events (TEAEs) over the first month following CAR T cell infusion for all 27-treated patients can be found in Table 2 (i.e., before pembrolizumab treatment).

Table 2: Mesothelin Study: TEAEs in ≥15% of Patients Over First Month (Monotherapy; N=27)

Adverse Event Preferred Terms	Grade 1	Grade 2	Grade 3	Grade 4
Any TEAE	27 (100)	27 (100)	23 (85)	15 (56)
Hyperglycemia	27 (100)	12 (44)	3 (11)	0
Hypoalbuminemia	25 (93)	8 (30)	0	0
Anemia	24 (89)	15 (56)	6 (22)	0
Hypocalcemia	23 (85)	9 (33)	0	0
Hypomagnesemia	21 (78)	1 (4)	0	0
White blood cell decreased	19 (70)	16 (59)	13 (48)	9 (33)
Platelet count decreased	13 (48)	0	0	0
Fatigue	12 (44)	2 (7)	0	0
INR increased	12 (44)	1 (4)	0	0
Lymphocyte count decreased	11 (41)	15 (56)	16 (59)	6 (22)
Fever	9 (33)	5 (19)	0	0
Pain	8 (30)	5 (19)	0	0
Cough	8 (30)	0	0	0
aPTT prolonged	8 (30)	3 (11)	0	0
Malaise	5 (19)	0	0	0
Dyspnea	5 (19)	2 (7)	1 (4)	0
Cytokine release syndrome	5 (19)	2 (7)	0	0
Chills	4 (15)	0	0	0
Nausea	3 (11)	1 (4)	0	0
Constipation	2 (7)	1 (4)	2 (7)	0
Hypotension	1 (4)	3 (11)	0	0

TEAEs are listed in descending order in the proportion of patients with Grade 1 TEAEs.
aPTT=activated partial thromboplastin time; INR=International Normalized Ratio; TEAE=treatment-emergent adverse event.

The most frequently occurring TEAEs in >1 combination-treated patient up to 6 months following CAR T cell infusion can be found in Table 3.

Table 3: Mesothelin Study: TEAEs Over First 6 Months (CAR T cell + Pembrolizumab; N=18)

Adverse Events Preferred Terms	**Grade 1**	**Grade 2**	**Grade 3**
Any TEAE	15 (83)	7 (39)	2 (11)
Fatigue	6 (33)	0	0
Chest wall pain	5 (28)	2 (11)	0
Cough	4 (22)	1 (6)	0
Anxiety	3 (17)	0	0
Arthritis	2 (11)	0	0
Hoarseness	2 (11)	0	0
Dyspnea	1 (6)	2 (11)	0

TEAEs are listed in descending order in the proportion of patients with Grade 1 TEAEs.
CAR=chimeric antigen receptor; TEAE=treatment-emergent adverse event.

Overall, following CAR T cell infusion, a decrease in the incidence and severity of TEAEs observed at 6 months versus 1 month was demonstrated despite the addition of 3 doses of

pembrolizumab 200 mg Q3W. The combination arm included 18 of the 23 MPM patients. Notably, 7 of these patients (39%) had received ≥2 prior lines of therapy before CAR T cell infusion, and 3 of the 7 had received ≥3 prior lines of therapy. The median OS times were 23.9 vs 6.1 months for the combination (N=18) vs monotherapy (CAR T cell + cyclophosphamide; N=5) groups, respectively.

In summary, no DLTs or deaths were observed in the monotherapy or combination groups, and the incidence and severity of TEAEs over 6 months versus those observed at 1 month appeared to decrease despite the addition of pembrolizumab to CAR T cell therapy. Clinical activity was also markedly enhanced by the addition of pembrolizumab to CAR T cell monotherapy.

Another Phase 1/2 study using a CAR T cell treatment targeting CD19 and CD22 followed by limited duration pembrolizumab treatment in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL; Osborne 2020) yielded similar results. Three CAR T cell dose levels were investigated: 50, 150, and 450 x 10^6 total cells. Patients received CAR T cells alone, or with 3 doses of pembrolizumab 200 mg Q3W starting on Day 14 (regimen A), or with a single dose of pembrolizumab 200 mg on Day -1 (regimen B). As of Jan 21, 2020, dose escalation from 50 to 450 x 10^6 cells was completed with pembrolizumab regimen A and B without any observed DLTs. Across all dose levels, no severe CRS events were observed with primary infusion, with 5% of subjects having severe neurotoxicity (1/19), which resolved. There were no cases of severe CRS and no neurotoxicity of any grade at >50 x 10^6 cells. Overall, it was concluded that CAR T cells dose levels >50 x 10^6 used in combination with pembrolizumab induced complete responses (CRs) without severe CRS or neurotoxicities of any grade.

The combination of CAR T cells + pembrolizumab have also been safely used to treat 3 patients with neuroblastoma, with no DLTs being observed (Heczey 2017). In this case, PD-1 inhibition was not found to enhance CAR T cell expansion or persistence, and antitumor responses were modest. It was speculated low PD-1 expression levels on CD4 (≤20.6%) and CD8 (≤9.04%) CAR T cells and the presence of additional immune suppressive mechanisms may have led to these results (Heczey 2017).

Lastly, the clinical activity & safety of ICT01, an anti-BTN3A mAb which activates γ9δ2 T cells is being investigated as a monotherapy and in combination with pembrolizumab in patients with advanced solid tumors (De Gassart 2021). To date, the mAb/γδT cell + pembrolizumab treatment has been well-tolerated during the dose escalation phase, and cohort expansion is planned in multiple solid tumor types (SITC 36th annual meeting December 2021 & AACR 2022).

1.9.4. Protocol TAC01-HER2-03 (Status Update)

As of 23 April 2023, the Phase 1 monotherapy arm of the study was completed. 19 subjects with solid tumors were treated in Cohorts 1-4. Treatment with TAC01-HER2 displayed a manageable safety profile:

- One DLT event of Grade 3 pneumonitis was reported in 1 subject in Cohort 4.
- No neurotoxicity was reported.

- All subjects treated in Cohorts 3-4 experienced CRS, mostly Grade 1 or 2, which resolved with supportive therapy.
- Serious adverse events (SAEs) related to TAC01-HER2 consisted of 1 Grade 3 pneumonitis (as mentioned above), 1 Grade 3 CRS, 3 Grade 2 CRS and 1 Grade 1 CRS.
- Most adverse events were related to LDC or the underlying malignancy.

Efficacy Status:

As of 23 April 2023, a 67% disease control rate (DCR) was observed in Cohorts 2-4 at 4 weeks restaging after TAC01-HER2 infusion and up to 3 months. For gastric/GEJ subjects in Cohorts 2-4, DCR was 83%. Two subjects had an unconfirmed partial response (PR):

- At Cohort 2, one subject with gastric cancer (3+ HER2) had reduction of measurable disease of 35%. This subject subsequently had stable disease for 4 months after TAC01-HER2 administration.

- At Cohort 4, an unconfirmed PR was observed in a subject with GEJ (HER2 2+, FISH+) with 100% reduction of target lesion. This subject progressed 3 months after TAC01-HER2 infusion. This subject previously progressed on 4 prior lines of therapy, including trastzumab and trastuzumab/deruxtecan.

- Based on the clinical benefit observed for gastric/GEJ cancer in Phase 1 (33% ORR at Cohorts 2-4) and given the current standard of care (trifluridine/tipiracil with ORR 4%) (Shitara 2018), Triumvira decided to pursue these indications in Phase 2.

1.10. Lymphodepleting Chemotherapy Rationale

It is widely believed LDC improves engraftment and activity of genetically modified T cells. However, the mechanism by which T cell engraftment is facilitated by LDC is not fully understood. The rationale for combining adoptive T cell immunotherapy with lymphodepleting therapy is multifold.

First, LDC may enhance adoptively transferred tumor-specific T cells to proliferate in vivo through homeostatic proliferation (Grossman 2004, Stachel 2004). Second, chemotherapy may reduce or eliminate CD4-positive, CD25-positive regulatory T cells, which can suppress the function of tumor-targeted adoptively transferred T cells (Turk 2004). Third, LDC prior to adoptive T cell therapy may enhance the expression of stromal cell-derived factor 1 (SDF-1) in the bone marrow, enhancing the trafficking of modified T cells to the primary tumor site through binding of SDF-1 with C-X-C motif Chemokine Receptor 4 expressed on the T cell surface (Pinthus 2004). Finally, LDC leads to elimination of cytokine sinks (IL-2, IL-7, and IL-15) and increased expansion, function, and persistence of T cell therapies (Neelapu 2019).

In this study, LDC will consist of fludarabine or clofarabine and cyclophosphamide administered daily for 3 consecutive days. The combination of fludarabine or clofarabine and cyclophosphamide has been used for lymphodepletion in CAR T cell studies with demonstrable

CAR T cell expansion, persistence, and antitumor activity and acceptable safety (Abramson 2017, Kochenderfer 2015, Turtle 2016).

The order of preference for LDC regimen is summarized in Section 5.2.

1.11. 'Second Dose Rationale

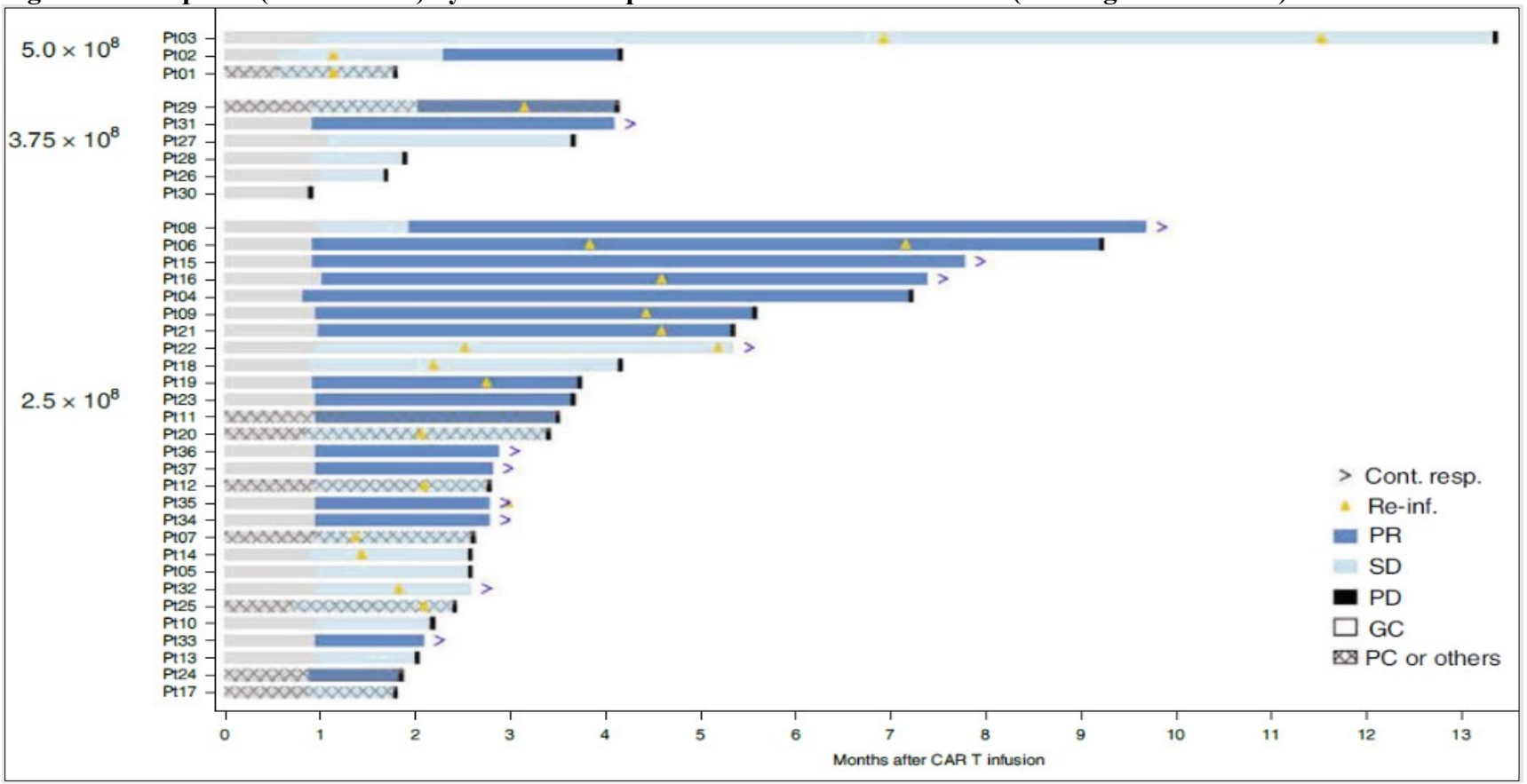
To date, cell therapies have struggled to induce durable responses in patients with solid tumors (Morotti 2021). Second infusions of engineered cells have been considered as an approach to improve TAC T cell trafficking, penetration, proliferation, and persistence to prolong the duration of clinical benefit for the longest duration possible. A recent Phase 1 study administered up to 3 equal doses of CLDN18.2-specific CAR T cells (CT041) in subjects with gastrointestinal cancer: 19/37 subjects (51.4%) received 1 dose, 15/37 (40.5%) received 2 doses, and 3/37 (8.1%) received 3 doses (Qi 2022). The median times to the second and third infusions were 72 and 101 days, with wide ranges (35-211 and 81-140, respectively). Overall, the most frequently reported Grade ≥3 TEAEs were lymphopenia (100%), leukopenia (83.3%), neutropenia (67.6%), increased conjugated bilirubin (21.6%), and thrombocytopenia (16.2%), with most being related to preconditioning treatments. These TEAEs generally occurred within 28 days after the first dose, with hematologic toxicities recovering between 4-9 days post dose. No Grade ≥3 CRS TEAEs were observed; however, 94.6% of subjects had Grade 1 or 2 CRS events. No clear dose response relationship correlated to the incidence of CRS events. No safety differences were described for subjects who received a single dose compared with subjects who received multiple doses.

Interim responses by subject and dose levels can be found in Figure 8. Most subjects treated with >1 dose showed longer duration of clinical benefit. Across all subjects, the median progression-free survival (PFS) was 3.7 months, with a high OS rate of 80.1% at 6 months (Qi 2022). Lastly, CLDN18.2 expression levels were found to be similar after the first infusion and before the second infusion, indicating antigen escape was not occurring. A similar Phase 1/2 study for CT041 is currently open in the US, which includes redosing of subjects (NCT04404595). One of the subjects in this study achieved a CR after 2 doses of CT041 during the dose escalation phase of the study (Botta 2022).

In addition, a Phase 2 trial of gavocel (genetically engineered T cells targeting mesothelin; NCT03907852) has incorporated in its design a second round of lymphodepletion and T cell administration (TCR2 Therapeutics). Subjects are re-dosed after they meet one of the following criteria: i) subjects with a confirmed response (CR or PR) that exhibit symptoms or signs of progressive disease (PD), or ii) subjects with stable disease (SD) for at least 8 weeks.

Additional doses are also applied for the treatment of hematological malignancies using allogeneic cell therapies. For example, a safety and efficacy study evaluating CTX110 (a CD19-directed CAR-T cell; NCT04035434), included re-dosing of subjects after disease progression.

Figure 8: Response (RECIST 1.1) by CLDN18.2-Specific CAR T Cells Dose Level (Investigator Assessed)



Source: Qi 2022.

CAR T=chimeric antigen receptor T cells; CLDN18.2=Claudin 18.2; Cont. resp.=continued response; GC=gastric cancer; PC=pancreatic cancer; PD=progressive disease; PR=partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1; Re-inf.=reinfusion; SD=stable disease;

Note: Yellow triangles indicate second and third doses, with the first dose administered on Day 1.

1.12. Statistical Design Rationale

Phase 1 Dose Escalation:

The dose finding part of this study will utilize the keyboard design (Yan 2017) to determine the safety and tolerability of various TAC01-HER2 dose levels in subjects with HER2+ solid tumors. The keyboard design is a novel Bayesian interval design that can be implemented in a simple way similar to the traditional 3+3 design but is more flexible and possesses superior operating characteristics. The keyboard design provides an upgrade to the modified toxicity probability interval (mTPI-2) design, with substantially lower risk of overdosing and a better precision to identify the maximum tolerated dose (MTD). Statistical analyses of the primary, secondary, and exploratory endpoints will be descriptive for the study. Summaries will be provided by dose level, overall, and by treatment arm. The incidence of DLTs, the incidence and severity of TEAEs, and laboratory abnormalities will be described and summarized. Subjects who are in DLT evaluation cohorts will be considered evaluable if they complete the defined DLT observation period.

Phase 2 Dose Expansion:

For Group A and Group B, a Simon 3-stage design will be used to evaluate potential efficacy responses, using predefined maximally ineffective and minimally effective ORRs derived from previous clinical studies (see Section 9.1 for additional details regarding the Simon 3-stage design and rationale for assumptions).

2. STUDY OBJECTIVES AND ENDPOINTS

Table 4: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1: To evaluate the safety of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	Incidence of DLTs Type, frequency, and severity of AEs (including clinically significant laboratory abnormalities).
Phase 2: To evaluate the clinical activity of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	ORR DOR OS DCR PFS or Time to progression (TTP) Investigator-assessed imaging using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
Secondary	
Phase 1: To determine the MTD or RP2D for TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	Incidence of DLTs
Phase 2: To evaluate the safety of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	Type, frequency, and severity of AEs (including clinically significant laboratory abnormalities).
Phase 1 and Phase 2: To characterize the PK profile of TAC01-HER2 in subjects with HER2+ solid tumors	Maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), and area under the concentration time curve (AUC) of TAC T cells Duration of persistence of TAC T cells
Phase 1: To evaluate the clinical activity of TAC01-HER2 monotherapy and pembrolizumab combination therapy in subjects with HER2+ solid tumors	ORR DOR OS DCR PFS or TTP Investigator-assessed imaging using RECIST 1.1

Phase 1 and Phase 2: To evaluate the immunogenicity of TAC01-HER2 monotherapy and pembrolizumab combination therapy and to assess potential impacts on PK exposure and biological activity	Immunogenicity of TAC T cells and pembrolizumab
Phase 1 and Phase 2: To investigate candidate efficacy biomarkers and anti-tumor activity of TAC T cells utilizing pre- and post-treatment tumor biopsies	Cytokines and TAC copies/ug genomic DNA (gDNA)
Exploratory	
Phase 1 and Phase 2: To explore biomarkers that may predict pharmacologic activity or response to TAC01-HER2 monotherapy and pembrolizumab combination therapy	Characterize T cells and correlate with clinical outcomes Describe profile of soluble immune factors and relationship to CRS, neurotoxicity, and TAC T cell engraftment

3. STUDY DESIGN AND INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a first-in-human study investigating TAC01-HER2 monotherapy and combination therapy with pembrolizumab to evaluate the safety, MTD or RP2D, PK parameters, and clinical activity in subjects with HER2+ solid tumors. During the Phase 1 portion of the study, increasing dose levels of TAC01-HER2 monotherapy will be evaluated first using the keyboard design method (Table 5).

Table 5: TAC01-HER2 Monotherapy Dose Escalation Schedule

Dose Level	TAC T Cells/kg body weight (Single Dose on Day 1)
-1	$6 – 8 \times 10^4$
1 (starting dose)	$1 – 3 \times 10^5$
2	$6 – 8 \times 10^5$
3	$1 – 3 \times 10^6$
4	$6 – 8 \times 10^6$

Once monotherapy dose escalation has been investigated, the safety data reviewed by the DSMC, and the RP2D is determined, combination therapy can begin in parallel with monotherapy dose expansion starting at a dose level that is 2 steps below the RP2D for TAC01-HER2. The RP2D has been determined by the DSMC to be Dose Level 4. Accordingly, the starting dose level will be Dose Level 2 (Table 6). The following TAC T cell dose levels will be investigated in the combination arm.

Table 6: Combination Therapy Dose Escalation Schedule

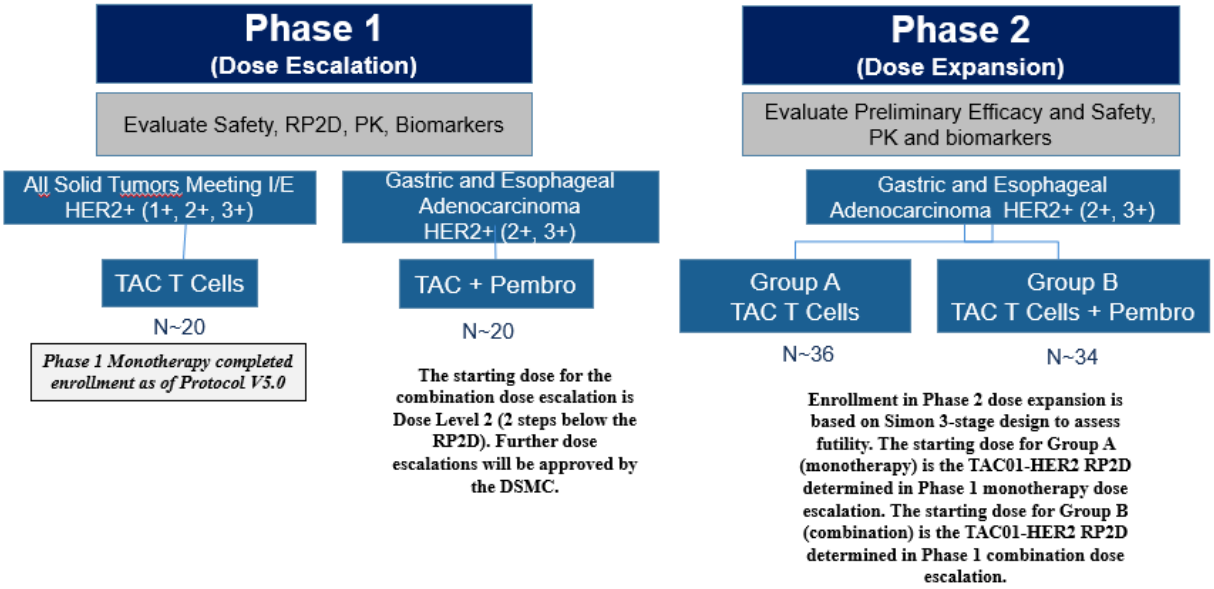
Dose Level	TAC T Cells/kg body weight (Single Dose on Day 1)	Pembrolizumab
1	$1 – 3 \times 10^5$	200 mg Q3W
2 (starting dose)	$6 – 8 \times 10^5$	200 mg Q3W
3	$1 – 3 \times 10^6$	200 mg Q3W
4	$6 – 8 \times 10^6$	200 mg Q3W

Subjects will be allocated to the group that allows the subject to start their treatment regimen in the shortest timeframe. Priority to enrollment will be for the combination dose escalation arm, with the following exceptions: within the safety gate interval, during DLT observation period, subject and Investigator preference, and if subject does not meet criteria to receive pembrolizumab.

As an additional safety precaution, the first combination cohort will treat 3 subjects with TAC T cells and administer pembrolizumab on Day 21. After review of safety data by the DSMC, and in the absence of DLTs, an additional 3 subjects will be treated at this same initial combination TAC T cell dose level, with pembrolizumab administered on Day 14. Based on the results of these 6 subjects, the DSMC will either recommend Day 21 or Day 14 for the start of pembrolizumab administration in all subsequent combination cohorts, followed by administration of pembrolizumab 200 mg Q3W for up to 2 years.

The overall study design is outlined in Figure 9. Phase 1 will evaluate increasing dose levels of TAC01-HER2 as a monotherapy, and in combination with pembrolizumab, to identify RP2Ds in subjects with HER2+ solid tumors who have progressed after 2 prior lines of therapy. In Phase 2, dose expansion groups will further evaluate the safety, clinical activity, and PK of the RP2D for TAC01-HER2 in subjects with HER2+ gastric and esophageal adenocarcinoma who have progressed after 2 and no more than 4 prior lines of therapy in 2 groups: **Group A** (TAC01-HER2 monotherapy) and **Group B** (TAC01-HER2 in combination with pembrolizumab). Central laboratory confirmation of HER2+ by IHC and fluorescent in-situ hybridization (FISH) will be conducted.

Figure 9: Study Design



Abbreviations: DSMC=Data Safety Monitoring Committee; HER2=human epidermal growth factor receptor 2; I/E=inclusion/exclusion; N=number of subjects; Pembro=pembrolizumab; PK=pharmacokinetics; RP2D=recommended Phase 2 dose; TAC=T cell antigen coupler.

In Phase 2, a second dose may be administered in the monotherapy arm (see Section 3.4 for additional details and Section 4.3 for eligibility criteria).

Upon enrollment, subjects will undergo leukapheresis to obtain T cells for TAC01-HER2 manufacture. Subjects may receive bridging anticancer therapy (see Section 5.1), after leukapheresis and before LDC if deemed necessary by the Investigator. Bridging therapies must be discontinued at least 14 days prior to initiation of lymphodepletion, and subjects must continue to meet eligibility criteria pertaining to adequate organ function (except hematologic parameters), active infections, pregnancy, measurable disease confirmed by repeat imaging, and medication washout before initiation of lymphodepletion. If TAC01-HER2 cannot be manufactured from the first leukapheresis product, additional leukapheresis may be allowed after consultation with Triumvira.

Upon the successful manufacturing of TAC01-HER2, subjects will enter the treatment phase. In the monotherapy arm, treatment will include LDC followed by a single dose of TAC01-HER2 administered IV on Day 1. In the combination arm, treatments will include LDC, a single dose of TAC01-HER2 administered IV on Day 1, and pembrolizumab 200 mg administered IV Q3W starting on Day 21 or Day 14 based on recommendations from the DSMC.

Subjects who receive 1 dose and subjects who receive combination therapy will follow procedures described in Appendix A1 and Appendix A2, respectively, for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up. Radiographic disease assessments for PD and other responses in single-dose subjects will occur

at Day 29±2 days, then Q8W±2W for Year 1 and Q12W±2W for Year 2. If a single-dose subject has initial PD on the Day 29 scan, a confirmation scan should occur 28 days (± 14 days) later to confirm the initial PD was not a tumor flare.

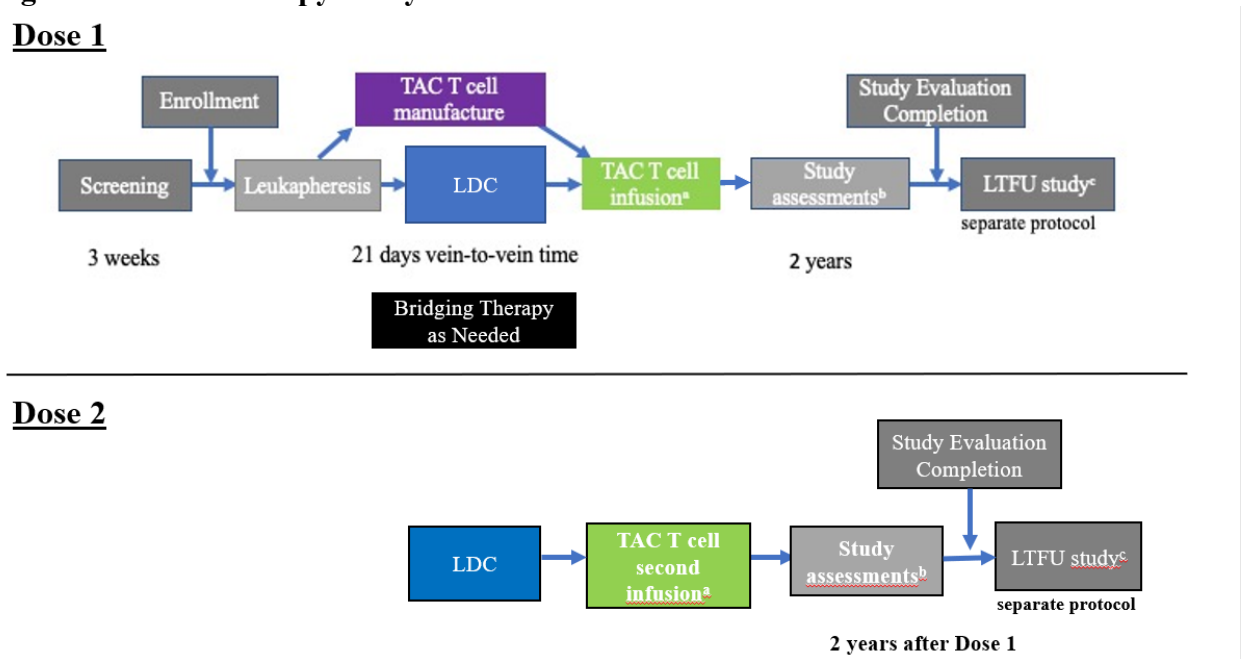
Subjects who receive 2 doses will follow procedures described in Appendix B for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow--up. Assessments for PD will occur on Day 29 ±2 days after the first dose on Day 1, then Q8W±2W until the second dose is administered. Once the second dose is administered (i.e., Day X), scans will be performed on Day X + 28 ±2 days, Q8W±2W after Day X for 1 year, and then Q12W±2W after Day X for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up.

If a subject has confirmed PD 3 months after the first dose, starts a new anticancer therapy, or is unwilling or unable to continue the respective procedures indicated in Appendix A1, Appendix A2, or Appendix B, then the subject will transition to the long-term follow-up (LTFU) protocol.

The LTFU protocol has a reduced schedule of events that complies with regulatory requirements for follow-up and does not include radiographic disease assessments. After study completion, subjects will be followed for survival, long-term toxicity, and viral vector safety to be monitored for up to 15 years.

The study sequence of events for the monotherapy arm is depicted in Figure 10.

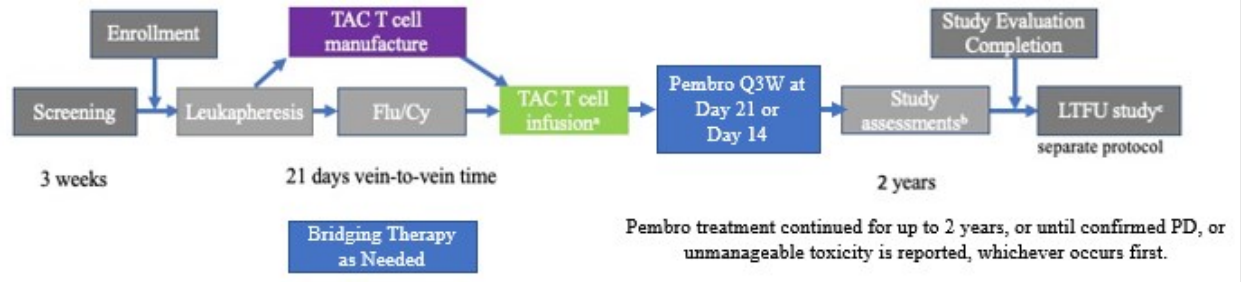
Figure 10: Monotherapy Study Scheme



Abbreviations: LDC=lymphodepleting chemotherapy; LTFU=Long Term Follow Up.
Bridging anticancer therapy is permitted if needed.
[a] TAC T cell infusion is considered Day 1 (Dose 1) or Day X (Dose 2) and described in Section 7.3.2.
[b] Study assessments are described in Section 7, Appendix A1, Appendix A2, or Appendix B.
[c] LTFU study is described in Section 7.8.

The study sequence of events for the combination arm is depicted in Figure 11.

Figure 11: Combination Therapy Study Scheme



Flow chart of the sequence of events according to the study design. Bridging anticancer therapy is permitted if needed. Abbreviations: FLU=fludarabine; CYC=cyclophosphamide; LTFU=Long Term Follow Up; PD=progressive disease; Pembro=pembrolizumab; Q3W=every 3 weeks.

3.2. Phase 1 Dose Escalation

The TAC01-HER2 dose levels to be evaluated in the monotherapy arm are provided in Table 5, with the combination doses provided in Table 6. Dose escalation/de-escalation will follow the keyboard design with a target DLT rate of 30% and an equivalence interval of 25% to 35%. The

keyboard table in Appendix C provides the dose escalation and de-escalation guidelines based on the number of subjects treated at a dose level who experience a DLT. Dose escalation may be halted once a dose level with acceptable safety and satisfactory antitumor activity has been selected for evaluation in Phase 2. A MTD may not be defined in this study.

The keyboard design is a seamless improvement to the mTPI-2 design, offering better overdose control and higher accuracy to identify the true MTD. For the mTPI-2, 3 decision intervals are specified after determining an estimated probability of toxicity (i.e., DLT). The 3 intervals are associated with dosing decisions (escalation, stay, or de-escalation). The probability of toxicity for each dose level is assumed to have an independent beta distribution. The mTPI-2 approach utilizes all subjects at the current dose level, as well as the total number of DLTs observed at that particular dose level to compute the normalized posterior probability in each interval in order to make subsequent dosing decisions. A normalized posterior probability statistic for each interval is calculated and is known as the unit probability mass (UPM). The largest UPM determines the dosing decision for the next cohort of subjects to be treated.

Similar to the mTPI-2 design, the keyboard design relies on the posterior distribution of the toxicity probability to guide dose escalation and de-escalation. The innovation is that the keyboard design defines a series of equal-width dosing intervals (or keys) to present the potential locations of the true toxicity of a dose and guide the dose escalation and de-escalation, whereas the mTPI design uses the UPMs of 3 dosing intervals (i.e., underdosing, proper dosing and overdosing intervals) to determine the dose transition.

The keyboard design requires pre-specification of the target toxicity rate (p_{target}) and the target toxicity interval $T_{target}=(p_{target}-\varepsilon 1, p_{target}+\varepsilon 2)$ (referred to as the target key). For this study, the pre-defined values of these parameters are $p_{target}=0.30$, $\varepsilon 1=0.05$ and $\varepsilon 2= 0.05$. Thus, the target toxicity interval is [0.25, 0.35] with a target toxicity of 0.30. Values lower than 0.25 would indicate that on average the probability of observing a toxicity at this dose level is too low based on our target probability, while those higher than 0.35 would be considered unacceptable toxicity. Since no prior information allows an accurate representation of the toxicity distribution, a non-informative beta (1, 1) distribution was assumed for the prior, which allow the results to be influenced more by the observed toxicity findings than the assumed distribution.

The keyboard design divides the target toxicity interval into a series of equally sized keys that span the range of 0 to 1. The decision to escalate or de-escalate the dose, given the observed data, is based on the "strongest" key that has the highest posterior probability (i.e., the largest area under the posterior distribution curve of the DLT rate for the current dose). By continuously identifying the strongest key T_{max} after each cohort, the dose assignment rules for the next cohort are:

- If the strongest key is on the left side of the target key ($T_{max} < T_{target}$), then escalate) to the next dose;
- If the strongest key is the target key ($T_{max} – T_{target}$), then stay (S) at the current dose;
- If the strongest key is on the right side of the target key ($T_{max} > T_{target}$), then de-escalate (D) to the previous dose.

A dose level with an unacceptable high toxicity level (probability >0.95) will result in de-escalation and will not be revisited. In addition, the study may be terminated based on the following criteria:

- Toxicity at the lowest dose level is determined to be higher than the acceptable toxicity level, or
- Sample size of 20 is reached.

Other reasons for terminating the study early may be applicable depending upon the toxicity and/or safety considerations. Following study completion, the MTD may be calculated using accumulated information for all dose levels. Refer to Appendix C for operating characteristics of this design.

In the monotherapy arm, for a dose level to be considered safe, at least 3 DLT-evaluable subjects must have completed the 28-day DLT evaluation period and the level estimated to be safe per the keyboard algorithm. In the combination arm, for a dose level to be considered safe, at least 3 DLT-evaluable subjects must have completed the 42-day or 35-day DLT evaluation period, depending on if pembrolizumab was dosed on Day 21 and 14 respectively, and the level estimated to be safe per the keyboard algorithm. The decision to open a dose level for enrollment will be made by the DSMC based on results from the keyboard algorithm.

The first 3 subjects in the monotherapy dose escalation will be treated with TAC01-HER2 at Dose Level 1 (1×10^5 to 3×10^5 TAC T cells/kg) and the first 3 subjects in the combination dose escalation will be treated with TAC01-HER2 at Dose Level 2 ($6 – 8 \times 10^5$), which is 2 steps below the monotherapy RP2D. Within the first dose cohort for monotherapy dose escalation and combination dose escalation, treatment of the second subject must occur a minimum of 28 days after the first subject's infusion. Treatment of the third subject must occur a minimum of 14 days after the second subject's infusion. Assuming no DLT is identified, subsequent subjects within this dose cohort may be treated without staggering. At each higher dose level, the interval between treatment of the first and second subject must also be staggered by at least 28 days. After staggering has been completed, no more than 1 subject may be treated with TAC01-HER2 in any dose cohort per day.

As indicated in the study design, once monotherapy dose escalation has been investigated, the safety data reviewed by the DSMC, and RP2D is determined, combination therapy can begin in parallel with monotherapy dose expansion using the dose level that is 2 steps below the RP2D for TAC01-HER2.

Overall, a minimum of 3 subjects will initially be treated at a dose level in the monotherapy and combination dose-escalation arms. If none of these 3 subjects experience a DLT, the dose will be escalated to the next higher dose level.

> However, there is an exception to this rule for the first combination treatment cohort **only**, where 3 subjects will be dosed with pembrolizumab on Day 21, and if after review of the safety data by the DSMC and no DLTs are observed, this same dose level will be investigated with pembrolizumab being administering on Day 14 with approval of the committee. If a DLT is observed in the first

combination cohort, where pembrolizumab is administered on Day 21, then the expansion combination cohort will not occur where pembrolizumab is administered on Day 14 at the same TAC01-HER2 dose. Instead, the following DLT-based dose directives based on the keyboard algorithm will continue to apply:

If 1 of 3 subjects experiences a DLT at a dose level, then additional subjects will be enrolled at this dose level and dose escalation/de-escalation decisions will be made per the keyboard algorithm after the DLT data for these additional subjects are available. If 2 of 3 subjects experience a DLT at a dose level, then the dose will be de-escalated to the next lower dose level. If all 3 subjects experience a DLT at a dose level, the dose will be de-escalated, and this dose and all higher doses will be removed from further evaluation in the study.

In the monotherapy dose escalation arm, a subject must have received TAC01-HER2 at the assigned dose, completed the 28-day evaluation period, or experienced a DLT prior to completing the 28-day evaluation period, to be considered evaluable for DLTs. Subjects who are not evaluable for DLTs will be replaced.

In the combination dose escalation arm, a subject must have received TAC01-HER2 at the assigned dose and pembrolizumab, as well as completed the 42-day or 35-day DLT evaluation period, depending on if pembrolizumab was dosed on Day 21 and 14 respectively, or experienced a DLT prior to completing the 42-day or 35-day evaluation period, to be considered evaluable for DLTs. Subjects who are not evaluable for DLTs will be replaced.

Based on the cumulative data from subjects treated in the dose finding phase, the MTD or RP2D will be selected for further evaluation in the dose expansion portion of the study. Once identified, an additional 3-6 subjects may be treated at the RP2D to confirm safety before proceeding to Phase 2. It is not necessary for the MTD to be determined per the keyboard algorithm to select the dose level to be evaluated in Phase 2.

Dose Limiting Toxicity Criteria

Toxicities will be evaluated and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (National Cancer Institute 2020), and CRS and neurotoxicity as per American Society for Transplantation and Cellular Therapy (ASTCT; Lee 2019) Consensus Grading as in Appendix D.

In the monotherapy arm, a DLT is defined as:

- Any Grade 4 or 5 event determined by the Investigator to be related to the investigational product, and not attributable to the underlying disease or LDC, with the exception of Grade 4 laboratory abnormalities (such as electrolyte abnormalities) that may be at least possibly related to the investigational product but are rapidly reversible or correctable without substantial safety concerns
- Grade ≥3 TAC T cell-associated acute infusion reactions persisting for ≥24 hours
- Grade ≥3 TAC T cell-associated CRS or neurotoxicity persisting for ≥72 hours
- Grade ≥3 cardiovascular or pulmonary toxicity persisting for ≥72 hours

- Grade ≥3 immune-related toxicities (i.e., colitis, nephritis, hepatitis, myocarditis, hypophysitis, salivary gland toxicity, etc.)
- Grade ≥3 organ toxicities or non-hematologic toxicities that do not improve to Baseline within 7 days
- Clinically consequential Grade ≥3 neutropenia or thrombocytopenia lasting ≥30 days from TAC01-HER2 administration. Clinically consequential is defined as febrile neutropenia, serious infection, or bleeding events.

In the combination arm, a DLT is defined as:

Definitions from the monotherapy arm that also apply to the combination arm:

- Any Grade 4 or 5 event determined by the Investigator to be related to the investigational product, and not attributable to the underlying disease or LDC, with the exception of Grade 4 laboratory abnormalities (such as electrolyte abnormalities) that may be at least possibly related to the investigational product but are rapidly reversible or correctable without substantial safety concerns
- Grade ≥3 TAC T cell-associated acute infusion reactions persisting for ≥24 hours
- Grade ≥3 TAC T cell-associated CRS or neurotoxicity persisting for ≥72 hours
- Grade ≥3 cardiovascular or pulmonary toxicity persisting for ≥72 hours
- Grade ≥3 immune-related toxicities (i.e., colitis, nephritis, hepatitis, myocarditis, hypophysitis, salivary gland toxicity, etc.)
- Grade ≥3 organ toxicities or non-hematologic toxicities that do not improve to Baseline within 7 days

Additional definitions of DLTs applicable to the combination arm:

- Any event that meets the definition of a DLT for the monotherapy arm that occurs before pembrolizumab administration, will prevent pembrolizumab administration (subject will be discontinued from combination arm and will follow the monotherapy schedule of events in Appendix A1).
- Grade 4 nonhematologic toxicity (not laboratory)
- Any new or worsening clinically significant Grade ≥3 neutropenia or thrombocytopenia lasting ≥7 days that develops ≤3 days after pembrolizumab administration despite best institutional corrective treatment measures
- Any Grade 4 hematological toxicity lasting ≥7 days after pembrolizumab administration despite best institutional corrective treatment measures
- 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 participant

    - The abnormality leads to hospitalization
    - 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 absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°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 participant to discontinue treatment during Cycle 1
- Grade 5 toxicity

DLT Evaluation Periods and Relatedness:

In the monotherapy arm, DLTs will be assessed from the time of the TAC01-HER2 infusion on Day 1 through 28 days post dose. The DLT evaluation period may be extended through 42 days post dose should clinically consequential (i.e., events associated with febrile neutropenia, serious infections, or bleeding) Grade ≥3 neutropenia or thrombocytopenia occur.

In the combination arm, DLTs will be assessed from the time of the TAC01-HER2 dose (Day 1) through Day 42 for cohorts that dosed pembrolizumab on Day 21, and through Day 35 for cohorts that dosed pembrolizumab on Day 14. In both scenarios, DLTs will include assessments over 1 cycle of pembrolizumab treatment (or 21 days after the initial dose of pembrolizumab).

DLTs that occur after TAC01-HER2 administration but before pembrolizumab treatment will be attributable to TAC01-HER2. DLTs that occur after pembrolizumab administration will be attributable to both study therapies. Since TAC01-HER2 is a single dose infusion, all DLTs or other adverse reactions observed after pembrolizumab administration will follow the guidelines for dose modification or discontinuation criteria listed in Appendix H and Appendix I.

The dose elimination rule in the keyboard design will be used as a stopping boundary for toxicity. Specifically, enrollment will be stopped if data indicate more than a 95% chance that the DLT rate exceeds 30%, corresponding to a strong signal that the RP2D previously selected was in error.

Summary of DLT Evaluation Periods with Possible Extensions:

As indicated in Table 7, only the monotherapy arm will have a 14-day extension of the DLT evaluation period if there are subjects with clinically consequential (i.e., events associated with

febrile neutropenia, serious infections, or bleeding) Grade ≥3 neutropenia or thrombocytopenia on Day 28. Also note, the following relevant DLT definition for the monotherapy arm:

- Clinically consequential (i.e., events associated with febrile neutropenia, serious infections, or bleeding) Grade ≥3 neutropenia or thrombocytopenia lasting ≥30 days from TAC01-HER2 administration.

Therefore, clinically consequential (i.e., events associated with febrile neutropenia, serious infections, or bleeding) Grade ≥3 neutropenia or thrombocytopenia prior to Day 30 will not be considered DLTs, as these AEs are always the result of LDC.

Table 7: DLT Evaluation Periods and Possible Extensions by Treatment Arm

ID	Treatment Arms	DLT Evaluation Period	DLT Extension due to Clinically Consequential Grade ≥3 Neutropenia or Thrombocytopenia
1	**Monotherapy Arm**	Day 1 through Day 28	Day 29 through Day 42 (or + 14)
2	**Combination Arm** for first pembrolizumab administration on Day 21	Day 1 through Day 42; 1 cycle of pembrolizumab after 1st dose, or 21 + 21=42	None
3	**Combination Arm** for first pembrolizumab administration on Day 14	Day 1 through Day 35; 1 cycle of pembrolizumab after 1st dose, or 14 + 21=35	None
4	**Combination Arm** for first pembrolizumab administration regardless of day of administration	New or worsening Grade ≥3 neutropenia or thrombocytopenia occurring ≤3 days after first pembrolizumab administration and lasting ≥7 days	None

3.3. Phase 2 Dose Expansion

In Phase 2, treatment with TAC01-HER2 will be evaluated both as monotherapy, and in combination with pembrolizumab, in subjects with gastric and esophageal adenocarcinoma. The monotherapy **Group A** will consist of up to 36 subjects (treated with TAC01-HER2 at the RP2D) following a Simon 3-stage design. The combination therapy **Group B** will consist of up to 34 subjects (treated with TAC01-HER2 at the RP2D) following a Simon 3-stage design (Figure 9).

All data from all available subjects (i.e., dose escalation and dose expansion phases) will be used when evaluating the potential efficacy of TAC01-HER2. Efficacy and safety of TAC01-HER2 will be determined both as a monotherapy and in combination with pembrolizumab. The primary

efficacy analysis for each arm will be based on all subjects who have measurable disease at the last disease assessment, prior to initiation of study treatments (i.e., TAC01-HER2 monotherapy or TAC01-HER2 + pembrolizumab combination therapy) and who receive TAC T cells at the RP2D. For further details on the planned statistical analysis, see Section 9.

The safety of TAC01-HER2 treatment in the monotherapy and combination arms will be monitored during Phase 2 to allow for adjustment of the RP2D dose or termination of enrollment in case the minimum threshold of clinical activity is not met.

3.4. Administration of Second Dose (Phase 2 Monotherapy Group Only)

A second dose may be administered >4 weeks from the date of the first dose. Administration of the second dose will be identical to the first dose and intrasubject dose escalation is not allowed. The >4 weeks are intended to allow for blood cell count recovery after initial LDC and ensure there are no residual toxicities related to immunogenicity resulting from the first dose. The purpose of the second dose is to improve TAC T cell trafficking, penetration, proliferation, and persistence and hence to prolong the duration of clinical activity for the longest duration possible. A second dose may be administered ≤1 year (to account for drug stability and study duration) from the date of the first dose.
Detailed eligibility criteria for the second dose are described in Section 4.3.

Ideally, the second dose should be administered within 2-3 weeks after the clinical criteria described in inclusion criterion #6 of Section 4.3 have been met, with LDC also being administered prior to the second dose. Subjects who progress on Day 29 ±2 days after the first dose and have confirmed PD 28 days ±14 days later are not eligible to receive a second dose. Subjects who progress at a later date are also not eligible to receive a second dose, unless their progression is documented as a mixed response (see Section 4.3 inclusion criterion #6 for the definition of a mixed response). If a subject experiences cytopenia that would preclude LDC administration and does not recover to Grade ≤2 within 7 days prior to LDC, a second dose may not be administered until recovery to Grade 2 given the subject did not experience confirmed radiographic disease progression.

3.5. Duration of Subject Participation

The study enrollment period is expected to take 21 months, and the follow-up period for each subject is approximately 24 months after TAC01-HER2 treatment on Day 1. Subjects in the monotherapy and combination therapy dose cohorts will continue the procedures indicated in Appendix A1, Appendix A2, or Appendix B, for up to 2 years, or until the subject withdraws consent, or the subject is lost to follow-up. If a subject has confirmed PD (i.e., with a confirmatory scan 28 days [± 7 days] after an initial scan indicating PD), or starts a new anticancer therapy, or the subject is unwilling or unable to continue the procedures indicated in Appendix A1, Appendix A2, or Appendix B, the subject will transition to the LTFU protocol. The LTFU protocol has a reduced schedule of events which complies with regulatory requirements for follow-up and does not include any radiographic disease assessments.

The time for an individual subject to complete the study is approximately 26 months, including Pre-Treatment (screening, leukapheresis, bridging anticancer therapy [if needed], and pre-treatment screening; collectively expected to be up to 2 months), Treatment #1, Treatment #2 (if criteria in Section 3.4 are met), and Post-Treatment Follow-Up (up to 24 months after Treatment #1). Thus, the total duration of the study will be approximately 50 months. All subjects who receive TAC01-HER2 treatment will be eligible to enroll in the LTFU protocol after completing this study (see Section 7.8), which includes follow-up for up to 15 years.

3.6. Subject Withdrawal from Study

During the informed consent process, subjects will be advised that they are free to withdraw from the study at any time for any reason; however, all subjects who receive monotherapy or combination therapy should be encouraged to continue all study evaluations through the end of study (EOS) visit and to participate in the LTFU study. Triumvira must be notified if a subject is withdrawn from the study and the reason(s) for withdrawal must be documented. Subjects who withdraw consent or are lost to follow-up will be followed for survival through publicly available records.

3.6.1. Subject Removal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Subject did not receive TAC01-HER2 due to disease-related complications
- Subject did not receive TAC01-HER2 due to interim treatment-related toxicities
- Subject no longer meets eligibility criteria for reasons unrelated to disease complications or interim treatment
- TAC01-HER2 could not be manufactured
- Subject withdrew consent
- Study termination by Triumvira, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or a regulatory authority
- Subject becomes lost to follow up
- Subject death
- Other

If a subject is withdrawn prematurely from the study, the reason for study discontinuation must be recorded in the subject's medical record and the case report form (CRF).

A subject who withdraws due to a failure to manufacture a TAC01-HER2 dose, who also meets the criteria for product release, may re-enroll in the study later if the subject meets all eligibility criteria.

3.6.2. Study Subject Replacement

Subjects in the dose finding phase who sign the informed consent form (ICF) but do not receive TAC01-HER2 in the monotherapy arm may be replaced, and those subjects who fail to receive

TAC01-HER2 or pembrolizumab in the combination arm may also be replaced. The reason(s) for not receiving TAC01-HER2 or pembrolizumab must be recorded in the subject's medical record and the CRF. Subjects in the dose finding phase who are not evaluable for DLTs may also be replaced (see Section 9.3.1.4 for the DLT-evaluable analysis set). Subject numbers will not be reused.

3.6.3. Subject Discontinuation Prior to Lymphodepleting Chemotherapy or Prior to TAC01-HER2 Dose

Subjects who undergo leukapheresis but do not receive LDC or TAC01-HER2 will remain on study and be followed for leukapheresis-related AEs and survival for at least 8 weeks, or until resolution of any leukapheresis-related AEs should they persist beyond 8 weeks. The same applies for subjects who receive LDC but fail to pass the pre-TAC01-HER2 treatment criteria.

3.7. Study Suspension or Termination

The study can be terminated at any time by Triumvira, the Health Authorities, or an IRB/IEC for any reason. Circumstances that may warrant suspension or termination include, but are not limited to:

- Identification of unexpected, significant, or unacceptable risks to subjects
- Determination of futility
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable

The Investigator may be informed of additional procedures to be followed to ensure adequate subject protection. The Investigator will be responsible for informing IRBs/IECs and any other local regulatory committee (as applicable) of the early study termination. Triumvira will be responsible for notifying any applicable regulatory authorities, such as the US Food and Drug Administration (FDA), of the early study termination.

If the study is suspended temporarily, it may resume once concerns about safety, protocol compliance, and data quality are addressed to the satisfaction of Triumvira, the DSMC, the IRB/IEC, and any applicable regulatory authorities.

3.7.1. Criteria for Study Interruption

The study will be paused pending notification of the DSMC and appropriate regulatory authorities if any of the following occur:

- Grade 4 toxicity attributable to TAC01-HER2 or pembrolizumab that is unexpected and unrelated to LDC
- Grade 4 neurotoxicity attributable to TAC01-HER2
- More than one Grade 4 CRS episode attributable to TAC01-HER2 during dose escalation
- Death related to TAC01-HER2 or pembrolizumab
- Death within 30 days of administration of TAC01-HER2 or pembrolizumab, unless clearly unrelated to the study and the product.
- Significant excessive toxicities, e.g., DLTs observed in >33% of subjects who received TAC01-HER2 or pembrolizumab (Phase 1 combination dose escalation cohorts only).

According to the pembrolizumab label, expected Grade 4 toxicities, including fever, hypotension, hypoxia, tumor lysis syndrome (TLS), and disseminated intravascular coagulation (DIC), will not require study interruption. In addition, the need for dialysis, and/or the need for mechanical ventilation are also expected. These expected toxicities may also result in secondary toxicities of Grade 4 renal toxicity, hepatic toxicity, or other organ involvement, which also would not lead to study interruption. Any Grade 4 toxicity that is not considered a DLT (refer to Section 3.2) will not lead to study interruption.

Adverse events observed after pembrolizumab treatment must be managed using the dose modification or discontinuation guidelines listed in Appendix H and Appendix I.

3.7.2. Criteria for Study Termination

The study will be terminated if any of the following occur:

- Any subject develops replication-competent lentivirus (RCL)
- Triumvira, IRB/IEC, or DSMC determines subject safety is compromised
- Triumvira discontinues development of TAC01-HER2

3.7.3. Continued Access to Pembrolizumab

Participants who are still on pembrolizumab at the time of study completion/termination may continue to receive study intervention if they are experiencing clinical benefit. The continued access to pembrolizumab will end when a criterion for discontinuation is met or 35 (for Q3W dosing) doses of pembrolizumab have been administered.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all the following criteria to participate in this study:

1. Signed, written informed consent obtained prior to any study specific procedures.

2. Age ≥18 years at the time of informed consent.

3. For Phase 1 and Phase 2:

   - Phase 1 monotherapy: HER2 1+, 2+, 3+ by IHC by central laboratory confirmation
   - Phase 1 combination: therapy: HER2 2+, 3+ by IHC and FISH by central laboratory confirmation
   - Phase 2 monotherapy (Group A): HER2 2+, 3+ by IHC and FISH by central laboratory confirmation
   - Phase 2 combination therapy (Group B): HER2 2+, 3+ by IHC and FISH by central laboratory confirmation

   In both phases, subjects who are HER2+ via recent (preferably after last line of therapy or within 1 year) tissue biopsy local laboratory results using IHC, FISH, or next generation sequencing (NGS) assays may also be enrolled, as long as a recent (preferably fresh or archival within 1 year) tissue biopsy sample is available for central laboratory HER2+ confirmation after enrollment and/or after starting TAC01-HER2. In the instance of discordant results between central and local laboratories (i.e., central laboratory results are negative with regards to IHC or FISH), the subject will still be considered evaluable for safety and evaluation of DLTs. In the instance of discordant results between central and local laboratories, the subject may be replaced in Phase 2.

   Central laboratory confirmation of HER2+ tumor samples will occur by one of the following methods (in order of priority; also see Section 7.2.3.1):

   a. A fresh tumor tissue sample, if clinically feasible and safe
   b. An archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1)
   c. A liquid biopsy to examine circulating tumor cells
   d. If a, b, or c are not obtainable, the most recent archival sample available regardless of when it was obtained during prior lines of therapy

   Fine needle aspirations, or brushing and scraping cytology samples, are not acceptable at Baseline or Screening. Since Phase 2 will be evaluating efficacy and since HER2 status often changes on progression after HER2-targeted therapies (e.g., trastuzumab), it is strongly recommended a fresh tumor tissue sample be obtained, if clinically feasible and safe, along with the corresponding pathology report for histological disease diagnosis confirming HER2-protein expression on the tumor cell surface.

4. Histologically confirmed advanced, metastatic, unresectable solid tumors (regardless of PD-L1 expression levels; Phase 1) and histologically confirmed advanced, metastatic, unresectable gastric or esophageal adenocarcinoma (regardless of PD-L1 expression levels for Phase 1 combination therapy and Phase 2) after at least 2 prior lines of therapy (Phase 1) or after at least 2 and no more than 4 prior lines of therapy (Phase 2). For the completed Phase 1 monotherapy subjects, HER2+ incurable malignancies for which no standard-of-care HER2 targeted therapy exists were enrolled regardless of the number of prior treatment lines, as long as in the opinion of the investigator the subject would be unlikely to tolerate or derive clinically meaningful benefit from other available treatment options. For breast cancer subjects, both prior lines of therapy must have included HER2-targeted agents per current standard-of-care. Subjects in the Phase 1 combination arm and Phase 2 can be enrolled if they have received less than 2 prior lines of therapy if, in the opinion of the investigator, the subject would not derive meaningful clinical benefit from an additional line of therapy.

   Subjects with solid tumors with genetic alterations and mutations (such as BRAF, BRCA, EGFR mutations, and ALK translocation) where approved targeted therapies were available to their specific cancers must have been previously treated with such approved therapies or refused such approved targeted therapy for their cancers prior to enrollment, or in the opinion of the investigator would be unlikely to tolerate or derive clinically meaningful benefit from these standard-of-care therapies.

5. Measurable disease per RECIST 1.1 at time of enrollment. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. ECOG performance status of 0 or 1 at Screening.

7. Life expectancy of at least 12 weeks.

8. Adequate organ and bone marrow reserve function prior to leukapheresis for monotherapy and combination arms can be found in Table 8 and Table 9, respectively.

9. Recovery to Grade ≤1 or Baseline for any toxicities due to previous therapy.

   a. If a subject received major surgery, they must have recovered adequately from the procedure and/or complications from the procedure prior to starting TAC01-HER2 therapy.

   b. Toxicity that has not recovered to Grade ≤1 is allowed if it meets the inclusion requirements for laboratory parameters.

   c. For the combination arm only: Subjects with Grade ≤2 neuropathy may be eligible, as may subjects with endocrine-related Grade ≤2 AEs requiring treatment or hormone replacement.

10. Adequate vascular access for leukapheresis as per institutional guidelines

11. For women physiologically capable of becoming pregnant, agreement to use highly effective methods of contraception starting 28 days prior to study treatment and for 1 year after the TAC01-HER2 dose. For men who have partners physiologically capable of becoming pregnant, agreement to use an effective barrier contraceptive method and refrain from donating sperm during study treatment and for 1 year after the TAC01-HER2 dose.

12. Subjects who are hepatitis B surface antigen (HBsAg) positive are eligible if they have received hepatitis B virus (HBV) antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to enrollment. Note: Subjects should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

13. Subjects with history of hepatitis C virus (HCV) infection are eligible if HCV viral load is undetectable at Screening. Note: Subjects must have completed curative anti-viral therapy at least 4 weeks prior to enrollment.

Table 8: Adequate Organ Function Laboratory Values for the Monotherapy Arm

System	Laboratory Value
Hematologic [a]	
Absolute neutrophil count (ANC)	≥1,000.0/µL
Absolute lymphocyte count (ALC)	≥450.0/µL [d]
Platelets [a]	≥75,000.0/µL
Hemoglobin [a]	≥8.0 g/dL
Renal	
Creatinine **AND** Estimated glomerular filtration rate (eGFR) [b] **OR** measured creatinine clearance [c]	≤1.5 X upper limit of normal (ULN) **AND** ≥60.0 mL/min/1.73 m^2 **OR** ≥40 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 X ULN **OR** ≤3 x ULN in the presence of liver metastases **OR** In subjects with known Gilbert's disease, serum total bilirubin <3 mg/dL
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5 X ULN or, If liver metastases present ≤5 X ULN
Alkaline phosphatase (AP)	≤2.5 X ULN or ≤5 x ULN for subjects with liver metastases or bone lesions.
Coagulation	
International normalized ratio (INR) or prothrombin time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Respiratory	
Adequate respiratory reserve	Grade 0 or 1 dyspnea and peripheral oxygen (O_2) saturation of ≥92% on room air
Cardiac	
Echocardiogram (ECHO) or multigated acquisition (MUGA) Scan	Left ventricular ejection fraction (LVEF) ≥45%

[a] Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support.
[b] eGFR should be calculated per institutional standard.
[c] Creatinine clearance should be calculated per institutional standard.
[d] Subjects with an ALC below 450.0/µL should be discussed with Triumvira's Medical Monitor for assessment of suitability for high volume leukapheresis based on the subject's tolerance, underlying malignancy, and any latent effects from prior antineoplastic therapies.

Table 9: Adequate Organ Function Laboratory Values for the Combination Arm

System	Laboratory Value
Hematologic [a]	
Absolute neutrophil count (ANC)	≥1500/µL
Absolute lymphocyte count (ALC)	≥450.0/µL [d]
Platelets	≥100,000.0/µL
Hemoglobin [a]	≥9.0 g/dL or ≥5.6 mmol/L [a]
Renal	
Creatinine **AND** Estimated glomerular filtration rate (eGFR) [b] **OR** measured creatinine clearance [c]	≤1.5 X upper limit of normal (ULN) **AND** ≥60.0 mL/min/1.73 m^2 **OR** ≥40 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 X ULN **OR** ≤3 x ULN in the presence of liver metastases **OR** In subjects with known Gilbert's disease, serum total bilirubin <3 mg/dL
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5 X ULN or, If liver metastases present ≤5 X ULN
Alkaline phosphatase (AP)	≤2.5 X ULN or ≤5 x ULN for subjects with liver metastases or bone lesions.
Coagulation	
International normalized ratio (INR) or prothrombin time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Respiratory	
Adequate respiratory reserve	Grade 0 or 1 dyspnea and peripheral oxygen (O_2) saturation of ≥92% on room air
Cardiac	
Echocardiogram (ECHO) or multigated acquisition (MUGA) scan	Left ventricular ejection fraction (LVEF) ≥45%

[a] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥approximately 3 months).
[b] eGFR should be calculated per institutional standard.
[c] Creatinine clearance should be calculated per institutional standard.
[d] Subjects with an ALC below 450.0/µL should be discussed with Triumvira's Medical Monitor for assessment of suitability for high volume leukapheresis based on the subject's tolerance, underlying malignancy, and any latent effects from prior antineoplastic therapies.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Intolerant to any component of TAC01-HER2.
2. Prior treatment with any of the following:
    a. Adoptive cell transfer of any kind, including CAR T cells
    b. Gene therapy
3. Investigational medicinal product within 5 half-lives or 21 days prior to leukapheresis, whichever is shorter.
4. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccines are allowed.
5. mAb, including PD-1 and PD-L1, therapies within 21 days prior to leukapheresis.
6. Radiation within 28 days prior to leukapheresis. Palliative radiation is allowed up to 14 days prior to leukapheresis if additional non-irradiated lesions are present.
7. Chemotherapy or targeted small molecule therapy within 14 days prior to leukapheresis, or within 7 days prior to leukapheresis for erlotinib, gefitinib, afatinib, crizotinib, or tucatinib.
8. Colony stimulating factors, including granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin, and other hematopoietic cytokines, within 14 days prior to leukapheresis.
9. Immunosuppressive medication within 14 days and corticosteroid treatment <72 hours prior to leukapheresis, except for physiological replacement doses (<12 mg/m^2/24 hours) of hydrocortisone or equivalent and topical or inhaled steroids.
10. History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
11. Active inflammatory neurological disorders (e.g., Guillain-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis).

12. Active autoimmune disease (e.g., lupus, rheumatoid arthritis, Sjogren's syndrome) requiring systemic treatment (i.e., disease modifying agents, corticosteroids, or immunosuppressive drugs) in the past 2 years. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Active or uncontrolled hepatitis B or C (HCV ribonucleic acid [RNA] positive) infection or any history of or active human immunodeficiency virus (HIV) infection.

14. Uncontrolled, acute, or life-threatening bacteria, viral, or fungal infection. Subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible if no evidence of active infection, this includes COVID subjects.

15. Class III or IV heart failure (as defined by the New York Heart Association [NYHA]), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease within 6 months prior to Screening.

16. Cardiac arrhythmia not controlled by medical management.

17. Clinically significant thrombotic events within 6 months prior to leukapheresis and/or inability to stop anticoagulation for at least 2 half-lives prior to TAC01-HER2 infusion without compromising a subject's health.

18. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, non-metastatic squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

19. Pregnant or nursing (lactating). Females physiologically capable of becoming pregnant must have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test result at Screening and within 48 hours prior to initiating LDC.

20. As determined by the Investigator, any uncontrolled medical, psychological, familial, sociological, or geographical condition(s) that do(es) not permit compliance with the protocol.

21. Is currently participating in or has participated in a study using an investigational device within 4 weeks prior to the first dose of study treatment.

22. Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate, in the opinion of the treating investigator.

23. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Combination Arm Only Specific Exclusion:

24. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

25. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137), and was discontinued from that treatment due to a Grade 3 or higher immune-related AE (irAE).

26. Removed; combined with exclusion #10 (protocol Version 6.0).

27. Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of trial treatment.

28. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

29. Has history of an allogeneic stem cell transplant or a solid organ transplant.

30. Has a history of radiation pneumonitis. (Note: Cannot receive prior radiotherapy within 2 weeks of start of pembrolizumab. Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation [≤2 weeks of radiotherapy] to non-CNS disease; see Section 7.3.3).

4.3. Eligibility Criteria for Second Dose

4.3.1. Inclusion Criteria

1. ECOG performance status of 0 or 1 prior to second LDC.

2. Adequate organ function and bone marrow reserves prior to second LDC as shown in Table 8.

3. Completed 28 days of safety observation after the first dose to allow for any residual toxicity attributed to the initial dose to resolve.

4. No history of Grade ≥3 CRS or ICANS after receiving the first dose. Ongoing CRS or ICANS of Grade 1 or Grade 2 have resolved at least 7 days prior to the second LDC preceding the second dose.
5. Any Grade ≥3 cytopenias have resolved to Grade 2 at least 7 days prior to the second LDC preceding the second dose.
6. Fulfilled any of the following clinical criteria:

    - Subject has a confirmed RECIST 1.1 response (CR or PR) at the 3-month visit scans, who shows signs or symptoms of clinical progression that have been

documented by the Investigator (e.g., increase in tumor markers, decreases in performance status, significant sudden weight loss, ascites, effusion, increased intensity of cancer pain, etc.).

- Subject has an unconfirmed response (CR or PR) and shows signs or symptoms of clinical progression that have been documented by the Investigator (e.g., increase in tumor markers, decreases in performance status, significant sudden weight loss, ascites, effusion, increased intensity of cancer pain etc.).

- Subject has a mixed response; defined as measurable disease with reduction in size by at least 15% compared to baseline, with concurrent evolution of new lesions or enlargement of non-target lesions.

- Subject has SD at the 3-month visit scans, without turning into a response or who shows signs of clinical progression. For subjects with tumor growth above baseline on Day 29, but still within the margin of SD, a second dose may be administered.

4.3.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from receiving a second TAC01-HER2 dose:

1. Residual toxicities attributed to the initial dose that have not resolved to grade 2 or lower.

2. History of Grade ≥3 CRS or ICANS after receiving the first dose. Ongoing CRS or ICANS of Grade 1 or Grade 2 have not resolved at least 7 days prior to the second LDC preceding the second dose.

3. Grade 3 cytopenias that have not resolved to Grade 2 at least 7 days prior to the second LDC.

4. Unequivocal evidence of disease progression on Day 29 scans and confirmatory scans after the first dose.

5. Active severe infection

6. Pregnant until resolution or termination of pregnancy.

7. Date of first dose more than 1 year before administration date of second dose.

4.4. Contraception Requirements

TAC01-HER2 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Participants should be informed that taking the study medication may involve unknown risks to

the fetus (unborn baby) if pregnancy were to occur during the study. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

Any female subject who does not meet at least one of the following criteria will be considered physiologically capable of becoming pregnant:

- Post-menopausal for at least 12 consecutive months (i.e., no menses).
- Undergone a sterilization procedure (hysterectomy, salpingectomy, or bilateral oophorectomy). Tubal ligation is not considered a sterilization procedure.

Female subjects physiologically capable of becoming pregnant must have a negative serum pregnancy test at Screening and within 48 hours prior to starting LDC. Female subjects who are physiologically capable of becoming pregnant and are not sexually abstinent must agree to use two forms of birth control (one highly effective method and one additional method) before starting study treatment (at least 14 days prior to the initiation of study treatment for oral contraception), during study treatment, and for 1 year after receiving TAC01-HER2 and/or at least 120 days following the last dose of pembrolizumab.

Male subjects who are sexually active with females physiologically capable of becoming pregnant must agree to use a highly effective method of birth control before starting study treatment, during study treatment, and for 1 year after receiving TAC01-HER2. In addition, men should not donate semen or sperm for 1 year after the last dose of study treatment (i.e., TAC01-HER2 or pembrolizumab).

Highly effective forms of birth control include abstinence, intrauterine device (IUD), hormonal agents (birth control pills, injections, implants, patch), tubal ligation, and vasectomy. Additional effective forms of birth control include a male or female condom with or without spermicidal agent, or a diaphragm or cervical cap with spermicidal agent.

4.5. Screen Failures

Screen failures are defined as subjects who consent to participate in the study but do not meet all required eligibility criteria. A minimal set of screen failure data is required to ensure transparent reporting, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. These data include, screen failure reasons, eligibility criteria, and if applicable, any SAEs. Blood and tissue samples obtained during Screening for subjects who are determined to be screen failures may be used by Triumvira for exploratory research.

Subjects who do not meet the criteria for study participation (i.e., screen failures) may be rescreened if their situation changes.

5. STUDY THERAPIES

5.1. Therapy for Disease Control During TAC01-HER2 Manufacturing

The manufacturing and quality testing of TAC01-HER2 may take approximately 3 weeks following leukapheresis. During this time, subjects may receive short-term bridging anticancer therapy before LDC if deemed necessary by the Investigator.

Phase 1:

Since the dose escalation component of the study is primarily focused on the characterization of safety, evaluation of DLTs, and determination of the RP2D in a late-stage disease, heavily pretreated population, the following bridging anticancer therapies are allowed to slow the progression of the underlying malignancy:

- Platinum-based immunochemotherapy
- Standard-of-care (SOC) chemotherapy
- Other potential bridging regimens in consultation with the Medical Monitor include low dose anthracyclines and HER2-targeted agents. Antibodies and investigational agents must be discussed with the Medical Monitor to ensure a proper washout period prior to initiation of lymphodepletion.

Phase 2:

Since the dose expansion component of the study is primarily focused on the characterization and detection of anti-neoplastic clinical activity across gastric and esophageal adenocarcinoma at the RP2Ds, the following bridging anticancer therapies are allowed:

- Platinum-based immunochemotherapy
- SOC chemotherapy

HER2-targeted agents including investigational agents and antibodies are not allowed as a bridging therapy in Phase 2 due to potential confounding effects with the HER2-targeted TAC01-HER2 treatment.

Duration of bridging therapy is limited to a maximum of 4 weeks, unless discussed with the Medical Monitor. All therapies must be discontinued at least 14 days prior to initiation of lymphodepletion and the time from leukapheresis to lymphodepletion cannot exceed 8 weeks ± 1 week to allow for scheduling delays and coordination of subject potential travel. Subjects must have recovered from bridging therapy-related toxicities to Grade ≤2 (except for alopecia) prior to initiation of lymphodepletion. Subjects who cannot receive lymphodepletion within 8 weeks ± 1 week after leukapheresis must be rescreened.

Palliative radiation is permitted following discussion with the Medical Monitor.

Also, a short course of 40 mg dexamethasone (≤4 days) or equivalent for emergency use for palliation of symptoms is allowed after previous consultation with the Medical Monitor.

If bridging anticancer therapy is necessary, appropriate disease measurements (e.g., CT scan) must be conducted or repeated prior to lymphodepletion to ensure the subject has measurable disease prior to initiating lymphodepletion. Subjects who respond to bridging anticancer therapy and may no longer have measurable disease must wait until their disease becomes measurable to be considered for monotherapy or combination arms of the study.

5.2. Lymphodepleting Chemotherapy

TAC01-HER2 will be administered as a single IV infusion approximately 72 hours after completion of LDC. Central venous access is recommended for the infusion of TAC01-HER2.

LDC will preferentially consist of 3 consecutive days of fludarabine or clofarabine and cyclophosphamide with or without mesna IV. If fludarabine or clofarabine is unavailable (due to national shortages), subjects can be treated with 3 consecutive days of cyclophosphamide with or without mesna IV or with bendamustine for subjects who cannot tolerate cyclophosphamide.

The LDC regimen, in order of preference, will consist of:

1. 3 consecutive days of fludarabine (30 mg/m^2 IV) and cyclophosphamide (300 mg/m^2 IV) with or without mesna IV.

2. 3 consecutive days of clofarabine (52 mg/m^2 IV) and cyclophosphamide (300 mg/m^2 IV) with or without mesna IV, if fludarabine is not available due to national shortages.

3. 2 consecutive days of bendamustine (90 mg/m^2) for subjects who cannot tolerate cyclophosphamide.

4. 3 consecutive days of cyclophosphamide (300 mg/m^2 IV) with or without mesna IV, if fludarabine or clofarabine is unavailable.

The dose intensity of either the primary (fludarabine or clofarabine + cyclophosphamide) or backup (cyclophosphamide or bendamustine) regimens can be modified based on a subject's CBC and creatinine clearance, upon discussion with the Medical Monitor.

The last dose of LDC should be administered approximately 72 hours (± 24 hours) prior to TAC01-HER2 administration. Ideally, LDC will be administered Days -4 through -2, Day -1 is a recovery day (there is no Day 0 in this protocol) and TAC01-HER2 infusion occurs on Day 1. A window up to 5 days is acceptable between completion of LDC and TAC01-HER2 infusion.

Delay of LDC by more than 14 days from its initially planned start requires discussion with the Medical Monitor and may require rescreening. Subjects who cannot receive lymphodepletion within 8 weeks ± 1 week after leukapheresis must be rescreened.

Antiemetic therapy, except dexamethasone or other low dose steroids, may be given prior to LDC per institutional practice.

Refer to the most recent package inserts for further details on the administration of these agents.

5.3. TAC01-HER2 Infusion

If a subject receives anticoagulation agents, therapy should be stopped at least 2 half-lives prior to TAC01-HER2 infusion and can be restarted 10 days after infusion. If neurotoxicity occurs, anticoagulation agents should be withheld until neurotoxicity has improved to Grade ≤1.

5.3.1. Dosage Form

The TAC01-HER2 product is a suspension of genetically modified autologous T cells expressing TAC-HER2 for infusion containing 10% DMSO in approximately 20 mL.

5.3.2. Administration

TAC01-HER2 will be administered as an IV infusion approximately 72 hours after completion of LDC.

Central venous access is recommended for the infusion of TAC01-HER2. The subject's identity must match the subject identifiers on the TAC01-HER2 product bag.

The tubing should be primed with normal saline prior to infusion, and TAC01-HER2 should be infused within 30 minutes. After infusion of the TAC01-HER2, the tubing should be flushed with normal saline to ensure all product is delivered. See Product Administration Manual for details.

In the event CRS or neurologic toxicities associated with this product class are observed, tocilizumab and emergency equipment must be readily available prior to infusion and during the recovery period. In case of a tocilizumab-shortage, as per institutional cell therapy guidelines anti-interleukin (IL) agents siltuximab or anakinra can be used instead.

5.3.3. Premedication

For TAC01-HER2, all subjects will receive acetaminophen (650 mg by mouth [PO] or IV) or diphenhydramine (25 to 50 mg PO or IV) or both at the discretion of the Investigator. These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids is not allowed.

5.3.4. Dosing Regimen

Each subject-specific single infusion bag will contain a dose of HER2-targeted viable TAC T cells as outlined in the Product Administration Manual.

5.3.5. How Supplied

Following completion of manufacture, the TAC01-HER2 product will be stored at the manufacturing site in the vapor phase of liquid nitrogen in a continuously monitored storage tank at or below -135°C. At the time of shipment, the cryopreserved dose(s) will be placed in a validated charged liquid nitrogen dry shipper equipped with a continuous temperature monitor. The investigative site will be notified of the shipment and tracking number used.

Prior to administration, the product will be thawed at or near bedside.

Additional TAC01-HER2 product details are provided in the TAC01-HER2 Product Administration Manual.

5.3.6. Non-Conforming Product

TAC01-HER2 that meets the specified release criteria for safety, identity, and purity but is non-conforming to the assigned dose for a subject may be released for administration. The product deviation plan defines the assessment and decision-making process, whereby a recommendation can be made to treat a subject with a TAC01-HER2 product that does not meet the specified release criteria for dose.

5.4. Pembrolizumab Infusion

5.4.1. Dosage and Administration

Pembrolizumab will be administered 200 mg IV for 30 minutes (-5 minutes/+10 minutes). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes [-5 minutes/+10 minutes]).

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

For pembrolizumab, Triumvira will provide it at no cost to the subjects, and it will be in the form of injection: 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

5.4.2. Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab combination 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 combination treatment, 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. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab can be found in Appendix H.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to TAC01-HER2 alone, or to pembrolizumab alone, for adverse events listed in Appendix H, both interventions must be held according to the criteria in Appendix H. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune related, pembrolizumab should be held according to recommended dose modifications.

Restarting Study Interventions:

Subjects may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Appendix H. If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from pembrolizumab.

If the toxicities do resolve and conditions are aligned with what is defined in Appendix H, pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to TAC01-HER2 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with, and agreement by, Triumvira.

5.4.3. 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 reaction can be found in Appendix I.

5.4.4. Other Allowed Dose Interruptions for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention.

However, study intervention is to be restarted within 3 weeks or 21 days for Q3W dosing of the originally scheduled dose and within 42 days for Q3W dosing of the previously administered dose, unless otherwise discussed with Triumvira. The reason for interruption is to be documented in the subject's study record.

5.4.5. Preparation and Storage

Directions for the preparation of pembrolizumab (IV infusion), storage of the diluted solution, and administration rate and method can be found in Section 2.4 of the current USPI and the preparation and administration section of the current Canadian Product Monograph. Storage and handling of pembrolizumab can be found in Section 16 of the USPI.

5.4.6. How Supplied

Pembrolizumab will be provided by Triumvira. Shipping details for pembrolizumab are provided on the pembrolizumab order request form.

5.5. Overdose

Overdose, as defined for this protocol, refers to LDC (with fludarabine/cyclophosphamide, clofarabine/cyclophosphamide, single agent cyclophosphamide, single agent bendamustine), pembrolizumab, or TAC01-HER2.

On a per-dose basis, an overdose is defined as:

- IV: 10% over the protocol-specified dose.

On a schedule or frequency basis, an overdose is defined as:

- Anything more frequent than the protocol-required schedule or frequency.

On an infusion rate basis, an overdose is defined as:

- Any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported on the CRF. See Section 8.2.1. for the reporting of AEs associated with overdose.

Pembrolizumab Overdose:

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

5.6. Supportive Care, Additional Treatment, and Monitoring

LDC should be administered as per institutional standard. To monitor and manage any potential toxicities, hospitalization is required for all subjects prior to treatment with TAC01-HER2. **Subjects should be hospitalized as per institutional cell-therapy guidelines for the day of infusion. Based on the Investigator's judgement, the subject may be asked to remain within approximately 1 hour of the investigative site for 28 days after infusion with TAC01-HER2.** Subjects and their caregivers must be instructed on the possible signs of early CRS, neurotoxicity, HLH, and MAS prior to treatment.

Prophylactic treatment/measures are strongly recommended for subjects at risk for TLS, per institutional standards.

Supportive care for CRS, neurotoxicity, HLH, and MAS management is detailed in Appendix E. Subjects who develop fever should be evaluated for infection and monitored for CRS.

The use of red blood cells and platelet transfusions, and/or colony-stimulating factors is permitted after determination of eligibility at initial Screening, per institutional or clinical standards. However, filgrastim (G-CSF) and GM-CSF are prohibited starting 14 days prior to leukaphereses and 7 days prior to TAC01-HER2 infusion until 5 days after the infusion. Cytopenias can emerge as late as 7 days after completion of LDC.

The use of prophylactic or empiric anti-infective agents is permitted per institutional standards. Prophylaxis may be provided for lymphopenia and/or neutropenia.

5.7. Concomitant Medications

5.7.1. Reporting Periods

Reporting periods for concomitant medications are summarized in Table 10.

Table 10: Reporting Periods for Concomitant Medications

Reporting Period	What to Record/Report
Informed consent to leukapheresis	Medications taken at the time of AEs/SAEs related to protocol-mandated procedures.
Leukapheresis to start of lymphodepleting chemotherapy	Medications taken at the time of AEs related to protocol-mandated procedures and at the time of any SAE.
Start of lymphodepleting chemotherapy to 90 days post-TAC01-HER2 dose	All medications.
Monotherapy Arm Only: 91 days post-TAC01-HER2 dose to end of study	Corticosteroids, anticancer therapies, and medications used to treat TAC T cell related AEs/SAEs.
Combination Arm Only: 91 days post-TAC01-HER2 dose to end of treatment with pembrolizumab	All medications.
Combination Arm Only: After end of treatment with pembrolizumab to end of study	Corticosteroids, anticancer therapies, and medications used to treat TAC01-HER2 or pembrolizumab-related AEs/SAEs.

5.7.2. Concomitant Medications During Hospitalizations

The following medications **should not** be recorded on the Concomitant Medication CRF during inpatient hospitalizations:

- IV fluids (except boluses used to treat CRS, which should be recorded)
- Heparin flushes
- Stool softeners
- Vitamins, minerals, health supplements
- Saline
- Lotions

The following treatments **should** be recorded on the Concomitant Medication CRF during inpatient hospitalizations:

- Vasopressors
- Oxygen use
- Corticosteroids

5.8. Prohibited Medications

G-CSF and GM-CSF are prohibited starting 14 days prior to leukapheresis and 7 days prior to TAC01-HER2 infusion until 5 days after the infusion.

Steroids are prohibited until disease progression or 2 years following TAC01-HER2 treatment, whichever comes first. Therapeutic doses of corticosteroids (defined as >20 mg/day prednisone or equivalent) must not be administered within 72 hour prior to leukapheresis and 72 hours before TAC01-HER2 administration. After TAC01-HER2 infusion, administration of therapeutic doses of corticosteroids is not permitted unless used for treatment of Grade ≥2 CRS or any grade of neurotoxicity or to modulate symptoms of an AE that is suspected to have an immunologic etiology. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated. Pre-treatment containing steroids may be given for necessary medications (e.g., IV immunoglobulin) after discussion with the Medical Monitor. Physiologic replacement steroids (≤12 mg/m^2/day hydrocortisone or equivalent [≤3 mg/m^2/day prednisone or ≤0.45 mg/m^2/day dexamethasone]), topical steroids and inhaled steroids are permitted.

The following medications are prohibited during the treatment and follow-up periods, unless used as an anticancer agent after inadequate response to TAC01-HER2 or disease progression:

- Anticancer agents, (excluding bridging anticancer therapy, LDC and agents used for treatment of uncontrolled TAC T cell proliferation or CRS.).
- Experimental agents.
- Definitive radiation (palliative radiation for cancer symptoms including pain management is permitted).
- Live or live attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Note: Killed vaccines are allowed. Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

6. POTENTIAL RISKS AND MANAGEMENT OF TREATMENT TOXICITIES

A discussion of potential TAC01-HER2 associated risks is available in the current TAC01-HER2 IB.

With regards to pembrolizumab potential treatment risks and management of toxicities, refer to Appendix H and Appendix I.

6.1. Cytokine Release Syndrome

With CAR T cell administration, CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee 2019), and management can be complicated by concurrent conditions. CRS symptoms appear a few days to weeks following administration of CAR T cells and may be severe and life-threatening (Lee 2019).

Fever (temperature ≥38.5°C or ≥101.3°F) is a commonly observed hallmark of CRS and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting

with CRS symptoms, appropriate cultures must be obtained, to exclude other causes for the fever, and empiric antibiotic therapy initiated per institutional standard of care.

Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, DIC, and capillary leak syndrome.

Neurological toxicity has been observed concurrently with CRS.

CRS has been reported in a few cases to be associated with findings of MAS/HLH, and the physiology of the syndromes may overlap. Subjects should be evaluated for the presence of other immune-related toxicities.

Refer to Appendix D for a detailed description of CRS management and treatment recommendations.

6.2. Myelotoxicities

Severe (Grade ≥3) and prolonged myelotoxicities, including anemia, leukopenia, neutropenia, and thrombocytopenia, may occur with either the LDC regimen and/or TAC01-HER2 administrations. CBCs should be monitored both prior to and after a TAC01-HER2 infusion. Institutional guidelines should be followed in the event of Grade ≥3 myelotoxicities.

6.3. Hypersensitivity Reactions

Allergic reactions may occur with infusion of genetically engineered T-cells such as TAC01-HER2. If hypersensitivity reactions occur, these reactions would be expected to happen during or immediately following the infusion, and may include bronchospasm, wheezing, angioedema, pruritus, and hives. Although unlikely, serious hypersensitivity reactions may occur, including anaphylaxis. Subjects should be monitored closely during and following the infusion. When a hypersensitivity reaction is suspected, discontinue the infusion and institute appropriate supportive care as needed, including bronchodilators and resuscitation procedures, as necessary.

6.4. Infusion Reactions

Infusion reactions may occur following administration of TAC01-HER2. If an infusion reaction were to occur, it would be expected to happen during or immediately following the infusion. Some infusion reactions may be related to the presence of DMSO in the formulation.

Infusion reactions can present with fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea. To minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen and/or diphenhydramine. Mild infusion reactions should be managed with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on TAC01-HER2's efficacy. Rigors may be treated with meperidine.

- The following guidelines should be followed for infusion reactions:

- **Grade 1:** Administer symptomatic treatment, continue TAC01-HER2 administration at the same dose and rate.
- **Grade 2:** Stop TAC01-HER2 administration, administer symptomatic treatment, and resume TAC01-HER2 administration at a reduced rate only after symptoms resolve.
- **Grade 3:** Stop TAC01-HER2 administration, administer symptomatic treatment, and resume TAC01-HER2 administration at a reduced rate only after symptoms resolve. If Grade 3 reaction recurs, discontinue TAC01-HER2 administration.
- **Grade 4:** Discontinue TAC01-HER2 administration and administer symptomatic treatment, as necessary.

6.5. Immune-Mediated Reactions

6.5.1. Pneumonitis

Monitor subjects for signs and symptoms of pneumonitis. Pneumonitis is considered an immune-mediated AE and may occur as an isolated event or may occur in association with CRS. If pneumonitis is suspected, evaluate with radiographic imaging, and exclude other etiologies. Institutional guidelines for corrective treatment measures should be followed in the event of pneumonitis.

6.5.2. Fever

Subjects who develop a fever (temperature ≥38.5ºC or ≥101.3°F) with or without neutropenia should be evaluated for infection (e.g., blood cultures obtained, imaging as clinically required for identification of potential source of infection) and treated with antibiotics, fluids, and other supportive care measures per institutional standard.

The possibility of CRS should be considered for all subjects with fever following TAC01-HER2 administration. Any onset of fever within the first 2 weeks after TAC01-HER2 administration should be evaluated with hospitalization for observation. Febrile subjects should be monitored closely for hemodynamic instability and changing neurologic status.

6.5.3. Neurologic Toxicities

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. According to published references, neurologic symptoms may begin 2 to 14 days after CAR T cell infusion and in severe cases may require admission to the Intensive Care Unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection (Kochenderfer 2015, Turtle 2016, Davila 2014, Gardner 2016, Maude 2014b). The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

Refer to APPENDIX C for a detailed description of neurotoxicity management and treatment recommendations.

6.5.4. Macrophage Activation Syndrome

MAS is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. There may be considerable overlap in clinical manifestations and laboratory findings between MAS and CRS. Subjects treated with TAC01-HER2 should be monitored for MAS, and cytokine-directed therapy should be considered as clinically indicated.

6.5.5. Tumor Lysis Syndrome

Both LDC and TAC01-HER2 may cause TLS. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover should receive prophylactic treatment per standard clinical practice.

6.5.6. Uncontrolled T cell Proliferation

TAC T cells, similar to CAR T cells, could theoretically proliferate out of control. If uncontrolled TAC T cell proliferation occurs, subjects may be treated with high-dose steroids (e.g., methylprednisolone 2 mg/kg/day, tapered over 2-3 weeks) or LDC doses of cyclophosphamide (1-3 g/m^2 IV). If an Investigator suspects uncontrolled TAC T cell proliferation, Triumvira should be contacted immediately.

6.5.7. Replication-Competent Lentivirus, Clonality, and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of RCL during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due, at least in part, to the use of self-inactivating vectors (Rothe 2014).

Concerns for possible vector integration into the host genome have arisen due to nonclinical studies that have shown retrovirus-mediated malignant transformation in mice (Li 2002, Modlich 2005) and monkeys (Donahue 1992), and a single clinical study reporting development of leukemia in subjects with X linked severe combined immunodeficiency (SCID) who received retroviral-modified CD34 positive hematopoietic stem cells (Hacein-Bey-Abina 2003), including 1 subject who died (Couzin 2005). Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or subjects have been reported to date.

Data have recently been published on the integration sites of retroviral and lentiviral vectors used for T cell modification in clinical studies (McGarrity 2013, Scholler 2012, Wang 2009). No clonality of integration sites was observed. In addition, there did not appear to be enrichment of integration sites near genes involved in clonal expansion or persistence.

Per the FDA guidelines (Testing of Retroviral Vector Based Gene Therapy Products Guidance 2020, Long Term Follow-Up After Administration of Human Gene Therapy Products Guidance 2020), all subjects treated with TAC01-HER2 will be followed for RCL and, if indicated, vector sequences for up to 15 years following TAC01-HER2 administration as part of the LTFU protocol. All subjects will be monitored for evidence of unexpected TAC01-HER2 expansion and the emergence of a new malignancy, particularly one of T cell origin. Investigators should contact Triumvira immediately if a new malignancy arises.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Schedule of Events

A monotherapy schedule of events (SOE) is provided in Appendix A1, with the combination therapy SOE provided in Appendix A2, and SOE for monotherapy subjects receiving 2 doses is provided in Appendix B. However, a very high-level summary is included as follows:

The study schedule is divided into 3 parts: Pre-treatment, Treatment, and Post-treatment.

Pre-treatment includes screening, leukapheresis, potentially bridging anticancer therapy and pre-treatment screening.

Monotherapy Treatment #1 includes LDC and TAC01-HER2 administration on Day 1, as well as follow-up through Day 29.

Monotherapy Treatment #2 includes LDC and TAC01-HER2 administration on Day X and post second dose procedures through Day X + 28 days.

Monotherapy Post-treatment Follow-up for subjects who receive 1 dose (Treatment #1) begins on Day 43 and lasts through Month 24 (calculated from the first dose Day 1), unless a subject has PD, starts a new anticancer therapy, withdraws consent, or is lost to follow-up. If these occur, the subject will be discontinued from this study and enrolled in the LTFU study.

Monotherapy Post-Treatment Follow-up for subjects who receive 2 doses (Treatments #1 and #2) begins on Day X + Day 43 and lasts through Month 24 (calculated from the first dose Day 1), unless a subject had PD, starts a new anticancer therapy, withdraw consent, or is lost to follow-up during this time. If these occur, the subject will be discontinued from this study and enrolled in the LTFU study.

Subjects who receive 1 dose (Phase 1 monotherapy) and subjects who receive combination therapy will follow procedures described in Appendix A1 and Appendix A2, respectively, for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up. Radiographic disease assessments for PD and other responses in single-dose subjects will occur on Day 29±2 days, then Q8W±2W for Year 1 and Q12W±2W for Year 2. If a subject who receives 1 dose has initial PD on the Day 29 (±2 days) scan, a confirmation scan should occur 28 days (± 7 days) later to confirm the initial PD was not a tumor flare.

Subjects who receive 2 doses will follow procedures described in Appendix B for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up. Assessments for PD will occur on Day 29 (±2 days) after the first dose on Day 1, then Q8W±2W until the second dose is administered in Year 1. Once the second dose is administered, (i.e., Day X), scans will be performed on Day X + 28±2 days, Q8W±2W after Day X for 1 year, and then Q12W±2W after Day X for up to 24 months after the first dose, until the subject withdraws consent, or the subject is lost to follow-up. If a subject who receives 2 doses has PD on the Day X + 28±2 days scan, no confirmation scan is required to confirm PD.

For subjects who receive 1 dose (Treatment #1), all subsequent visits/procedures/laboratory assessments will be based on Day 1, when the only TAC01-HER2 dose was administered.

For subjects receiving 2 doses (Treatments #1 and #2), all subsequent visits/procedures/laboratory assessments will be based on Day 1, except scans and those specifically designed to monitor PK and other laboratory assessments occurring 42 days after Day X, see Appendix B for clarity (e.g., Day X, X+5, X+8, X+15, X+29).

Combination Treatment includes LDC, a single dose of TAC01-HER2 on Day 1, and pembrolizumab administration on Day 21 or Day 14 and then continuing Q3W for up to 24 months.

Combination Therapy Post-treatment continues from the last dose of pembrolizumab through Month 24 unless the subject withdraws consent, or the subject is lost to follow-up. Subjects starting a new anticancer therapy should transition to the LTFU protocol.

All procedures and clinical laboratory assessments on days that LDC, TAC01-HER2, or pembrolizumab are administered must be performed pre-dose unless otherwise specified. Clinical laboratory assessments may be performed within 1 day prior to start of LDC, TAC01-HER2, or pembrolizumab administration. Results from clinical laboratory assessments must be reviewed prior to initiation of LDC, TAC01-HER2, or pembrolizumab administration.

The Month 24 visit will be the EOS visit unless a subject discontinues early.

Subjects who experience disease progression after the initial dose of TAC01-HER2 should complete the PD visit to confirm PD 28 days (± 7 days) after their initial PD scans. If confirmatory scans indicate PD the subject should be permanently discontinued from pembrolizumab, unless the subject is considered by the Investigator to derive clinical benefit, is clinically stable, and there is agreement from Triumvira. Clinical stability is defined by the following: absence of new symptoms and signs indicating clinically significant PD, no decline in ECOG performance status, absence of rapid progression of disease or progressive tumor at critical anatomical sites requiring urgent alternative medical intervention.

If a Day 29 (±2 days) PD is confirmed 28 days later (±7 days) after Dose 1 or a new anticancer therapy is initiated, the subject should transition to the LTFU protocol. For subjects who

withdraw from the study before the Month 24 visit, the EOS visit should be completed at the time of study withdrawal.

If subjects are not able to come to the investigational site for protocol specified visits due to the COVID-19 pandemic, alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local laboratory tests or imaging centers) may be implemented, when necessary, feasible, and sufficient to assure the safety of study participants. Any protocol deviations, missing data, or subject withdrawals related to COVID-19 must be documented.

7.2. Pre-Treatment

7.2.1. Screening

Screening will begin when the subject signs the IRB/IEC-approved ICF and continues until the subject is enrolled or is determined to be a screen failure.

The following assessments will be performed during screening:

- Eligibility assessment.
- Clinically significant medical history review, including disease diagnosis and history, hematopoietic stem cell transplant (HSCT) history if applicable, and chemotherapy, radiation, and surgical history. May include history of toxicities related to prior treatments and allergies.
- Physical examination, including neurological examination, vital signs, height, and weight within 2 weeks prior to enrollment.
- ECOG performance status assessment within 2 weeks prior to enrollment (see Appendix G).
- 12-lead electrocardiogram (ECG) (may be performed up to 8 weeks prior to enrollment).
- Cardiac echocardiogram (ECHO) or multigated acquisition (MUGA) scan (may be performed up to 8 weeks prior to enrollment).
- Local laboratory assessments (chemistry, coagulation, hematology, viral serology, serum pregnancy) within 2 weeks prior to enrollment.
- Tumor sample and pathology report availability confirmation.
- If a fresh biopsy is not feasible, then an archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1). If this is not feasible, a liquid biopsy to examine circulating tumor cells should be performed. Lastly, if this is not feasible, the most recent archival sample available regardless of when it was obtained during prior lines of therapy is acceptable.
- Record AEs/SAEs related to protocol mandated procedures and associated concomitant medications.

7.2.2. Leukapheresis

Following enrollment in the study, leukapheresis will be performed on each subject to obtain enough quantity of peripheral blood mononuclear cells (PBMCs) for the production of TAC01-HER2. If a technical issue arises during the procedure or in the immediate processing of the leukapheresis and it cannot be used for TAC01-HER2 production, the subject may have additional leukapheresis procedures performed. Further information is provided in the Leukapheresis Collection Manual.

The following assessments will be conducted on the day of leukapheresis:

- Peripheral blood sample collection for local clinical laboratory evaluations, including:
  - Hematology (CBC with differential)
  - Serum chemistry
  - Coagulation
- Hematology results must be evaluated prior to leukapheresis. To ensure results are available, the sample may be collected up to 24 hours prior to leukapheresis.
- Vital signs (before leukapheresis)
- Record all AEs related to protocol-mandated procedures, all SAEs, and concomitant medications.

7.2.3. Pre-treatment Screening and Baseline Evaluations

The subject must continue to meet eligibility criteria pertaining to adequate organ function except for hematologic parameters (platelet count of ≥30,000/mm^3 is permitted prior to LDC, but neutrophil count must be ≥1,000.0/µL, hemoglobin ≥8 g/dL, and absolute lymphocyte count [ALC] ≥450.0/µL), and also meet eligibility requirements for active infections, pregnancy, measurable disease, and washout of prior therapy before initiation of LDC (see Section 5.2). An adequate and recent set of scans must be available to serve as a baseline scan for tumor assessments that will be obtained post TAC01-HER2 infusion.

Pre-treatment screening (Baseline) evaluations must occur within 14 days prior to initiation of LDC and must occur after the completion of any bridging chemotherapy. For subjects who receive bridging chemotherapy with potentially cardiotoxic drugs, a repeat ECHO or MUGA scan must be performed within 7 days prior to initiation of LDC. Evaluations will be performed as indicated in the respective monotherapy and combination therapy SOEs (see Appendix A1, Appendix A2, or Appendix B).

7.2.3.1. Tumor and Correlative Studies Tissue Collection

All subjects enrolled into this study must be able to provide a newly obtained biopsy (fine needle aspirate is not adequate) to be submitted for characterization. If this is not clinically feasible and safe, subjects can instead provide an adequate archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1). If this is not feasible, the most recent archival sample available is acceptable.

Exploratory biopsies should be limited to percutaneous lesions that are palpable, or guided by imaging/endoscopy if necessary, and not be obtained from any lesions that are in proximity to vital visceral, cardio-pulmonary, or neurovascular structures. When feasible biopsy sites should be selected so that subsequent biopsies, if needed, can be performed at the same location. Tumor lesions that are inaccessible or contraindicated due to subject's safety concerns will not be biopsied.

For the Phase 1 portion of the trial, tumors must be HER2+ by IHC. For the Phase 2 portion of the trial, tumors must be HER2 2+ or 3+ by IHC and FISH.

Refer to the laboratory manual for additional details

7.2.4. Pre-treatment Evaluations for Phase 2 TAC01-HER2 Second Dose

The subject must continue to meet eligibility criteria pertaining to adequate organ function (Table 8) except for hematologic parameters (platelet count of ≥30,000/mm^3 is permitted prior to LDC, but absolute neutrophil count must be ≥1000.0/µL, hemoglobin ≥8 g/dL, and ALC ≥450.0/µL), and also meet eligibility requirements for second dose as described in Section 4.3.

Subjects who receive palliative radiation may receive a second dose but not those who receive curative radiation, or another systemic antineoplastic therapy, should be discontinued from the study and enrolled in the separate LTFU protocol. Anticoagulation requirements listed in Section 5.3 also apply to the second dose.

7.3. Study Treatments

7.3.1. Lymphodepleting Chemotherapy

Subjects should have a hemoglobin level ≥8 g/dL, a platelet count of ≥30,000/mm^3, and an ALC ≥450.0/µL prior to lymphodepletion; red blood cell transfusions and other supportive measures may be used.

The following assessments will be performed on each day of LDC, prior to administration of LDC:

- Physical examination, including routine neurological examination, vital signs
- Weight (first day only)
- ECOG performance status assessment (first day only)
- Local laboratory assessments, including hematology, coagulation, and serum chemistries. The assessments prior to the second and third day of LDC are to guide supportive care and medical decision making.
- Record all AEs and concomitant medications.

7.3.2. TAC01-HER2 Treatment

7.3.2.1. TAC01-HER2 Infusion Criteria (Day -1)

Note: For the second dose, Day -1 will be the study day before the second dose date

Treatment should be delayed for subjects who meet at least one of the following criteria within 24 hours prior to the scheduled TAC01-HER2 infusion:

- Significant worsening in clinical status in the Investigator's opinion and would increase the risk of TAC01-HER2 treatment-related AEs
- Suspected or active systemic infection
- Onset of fever ≥38.5°C/101.3°F not related to underlying disease
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New-onset or worsening of non-hematologic organ dysfunction Grade ≥3
- Taking any of the prohibited medications as described in Section 5.8

In the case of a delayed infusion, lymphodepletion may need to be repeated after discussion with the Medical Monitor.

7.3.2.2. TAC01-HER2 Infusion Day 1 (Dose 1 and 2)

TAC01-HER2 will be administered as described in Section 5.3.2. Evaluations will be performed as indicated in the respective monotherapy and combination therapy SOEs (see Appendix A1, Appendix A2, or Appendix B). Additionally, vital signs (see Section 7.13.4) will be measured within approximately 15 minutes (± 5 minutes) before and 15 minutes (± 5 minutes) after infusion, then approximately every 15 minutes thereafter for the first hour and hourly (± 15 minutes) for the next 3 hours. Thereafter, vital signs should continue to be monitored until stable and as clinically indicated.

7.3.3. Pembrolizumab (Starting Day 21 or Day 14 then Q3W; Combination Arm Only)

To receive pembrolizumab, subjects must have adequate organ function as defined in Table 9. Specimens must be collected within 10 days prior to the start of pembrolizumab. Window does not apply to ECHO/MUGA.

Subjects must not have received prior radiotherapy within 2 weeks of start of pembrolizumab. Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

If organ function is not adequate as defined in Table 9, a dose delay of the first dose of pembrolizumab of up to 14 days is allowed. If the subject still does not meet the adequate organ function criteria after the 14-day dose delay, the subject will be discontinued from the combination arm and will follow the monotherapy schedule of events in Appendix A1.

Pembrolizumab will be administered and monitored according to the USPI and the Canadian Product Monograph or per institutional standards-of-care (also see Appendix H and Appendix I), also see Section 5.4.1. Evaluations, examinations, imaging, and laboratory procedures will be performed as indicated in the SOE (Appendix A2).

7.3.4. Confirmed Disease Progression and Treatment Beyond PD (PD Visit)

The assessments listed for PD (Appendix A1, Appendix A2, or Appendix B) will be performed approximately 28 days (± 7 days) after disease progression is initially suspected by a primary (Day 29 ± 2 days) scan(s).

In monotherapy arms, if confirmatory scans indicated PD, the subjects should be enrolled in the LTFU protocol. Subjects who experience disease progression 28 days after the second dose do not require a confirmatory scan 28 days later and should be discontinued from the study and enrolled in the LTFU protocol.

In combination therapy arms, if confirmatory scans indicate PD, the subject should be permanently discontinued from pembrolizumab, unless the subject is considered by the Investigator to derive clinical benefit, is clinically stable, and there is agreement from Triumvira. Clinical stability is defined by the following: absence of new symptoms and signs indicating clinically significant PD, no decline in ECOG performance status, absence of rapid progression of disease or progressive tumor at critical anatomical sites requiring urgent alternative medical intervention. If the subject is permanently discontinued from pembrolizumab, the subject should be enrolled in the LTFU protocol.

7.4. Post-treatment Evaluations

See the respective SOEs for the monotherapy and combination treatment arms in Appendix A1, Appendix A2, or Appendix B. Subjects with confirmed PD and/or who start a new anticancer therapy should be followed according to the LTFU protocol.

7.5. Unscheduled Evaluations

If the Investigator determines that a subject needs to be evaluated at a time other than a protocol-specified visit, the subject may be asked to come into the clinic for an unscheduled evaluation. The following assessments, as well as any additional evaluations deemed appropriate by the Investigator, may be performed as clinically indicated:

- Physical examination
- Vital signs
- ECOG performance status assessment
- Clinical laboratory evaluations or tissue assessments
- Positron emission tomography (PET) and/or computed tomography (CT) scan or magnetic resonance imaging (MRI) if indicated
- Tumor biopsy
- Other

7.6. Subject Death and Autopsy

In the event of a subject's death, an autopsy may be requested as per institutional guidelines. If an autopsy is performed, tissue samples may be requested and sent to Triumvira for evaluation of the presence of TAC T cells in brain, liver, kidney, lungs, bone marrow, blood, heart, reproductive organs, and any sites of disease. Every effort will be made to assay for RCL in a sample of the pertinent autopsy tissue.

7.7. Early Withdrawal

If a subject withdraws prematurely from the study, an EOS visit will be scheduled as soon as possible, and all the assessments listed for the EOS visit (Appendix A1, Appendix A2, or Appendix B) will be performed. The reason for early withdrawal will be captured on the CRF.

7.8. Long-Term Follow-Up

Because this protocol involves gene transfer, follow up for lentiviral vector safety, disease status, and long-term survival will continue in this study until Month 24 and under a separate LTFU protocol for up to 15 years after TAC01-HER2 administration. For subjects who cannot or do not want to be followed for 24 months on the study protocol as per Appendix A1, Appendix A2, or Appendix B, the LTFU protocol outlines a reduced schedule of events that complies with regulatory requirements.

If a Day 29 (±2 days) PD is confirmed 28 days (± 14 days) after Dose 1 or if PD occurs any time at or after 28 days following Dose 2, or if a new anticancer therapy is initiated, an EOS visit should be conducted, and all subjects will enroll in the separate LTFU protocol. For subjects who withdraw from the study before the Month 24 visit (calculated from the first dose Day 1), the EOS visit should be completed at the time of study withdrawal.

7.9. Study Procedures

7.9.1. Administrative Procedures

7.9.1.1. Informed Consent

The Investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in this clinical study or Future Biomedical Research (FBR).

7.9.1.2. General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form will be given to the subject before participation in the study.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must receive the IRB/IEC's approval or favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participating in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/IEC requirements, applicable laws, regulations, and Triumvira requirements.

7.9.1.3. Consent for Future Biomedical Research

The Investigator or qualified designee will explain the FBR consent to the subject, answer all his/her questions, and obtain written informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the subject.

7.9.2. Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the study.

7.9.3. Subject Identification Card

All subjects will be given an IRB/IEC approved Subject Identification Card identifying them as participants in a research study. The card will contain study site contact information (including

direct telephone numbers) to be utilized in the event of an emergency. The Investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

7.10. Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered clinically significant by the Investigator. Details regarding the subject's cancer will be recorded separately and not listed as medical history.

7.11. Prior and Concomitant Medications Review

7.11.1. Prior Medications

The Investigator or qualified designee will review prior medication use and record prior medication taken by the subject within 28 days before starting the study. Treatment for the disease for which the subject has enrolled in the study will be recorded separately and not listed as a prior medication.

7.11.2. Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the subject during the study through the Safety Follow-up visit as outlined in Section 7.4. Record all medications taken for SAEs.

7.11.3. Prior Cancer Treatment Details

The Investigator or qualified designee will review all prior cancer treatments including but not limited to systemic treatments, prior transplantation, radiation, and surgeries and record in the study database.

7.12. Assignment of Subject Identification Number

All consented subjects will be assigned a unique subject identification (ID) number that will be used to identify the subject. Subject IDs will be assigned sequentially across the study; therefore, subjects within a single investigative site may not be sequential. Subjects will retain their assigned Subject ID from consent through study completion or screen failure. Subject IDs must not be re used for different subjects.

If a subject is enrolled and fails the pre-treatment Screening/Baseline evaluation, the subject will retain the assigned subject ID.

If a subject is re-screened prior to enrollment, a new Subject ID will be assigned; however, a link between the 2 Subject IDs will be maintained.

Specific details on the Screening visit requirements are provided in Section 7.2.

7.13. Clinical Procedures

7.13.1. Oncologic Disease Details

The Investigator or qualified designee will obtain prior and current details regarding oncologic disease status.

7.13.2. Full Physical Examination

The Investigator or qualified designee will perform a complete physical examination during the Screening period. At this visit, clinically significant abnormal findings should be recorded as medical history. A full physical examination should be performed during Screening and repeated as per the frequency defined in Appendix A1, Appendix A2, or Appendix B. After the TAC01-HER2 dose, new clinically significant abnormal findings should be recorded as AEs.

The neurological examination should include, at minimum, a physical examination to assess cranial nerves, motor and sensory skills, coordination, and balance.

7.13.3. Cardiac Evaluations

A standard 12-lead ECG will be performed, as well as an ECHO or MUGA scan using local standard procedures at Screening. Clinically significant abnormal findings should be recorded as medical history.

7.13.4. Vital Signs

The Investigator or qualified designee will take vital signs as specified in Appendix A1, Appendix A2, or Appendix B. Vital signs should include temperature, pulse, respiratory rate, oxygen (O_2) saturation by pulse oximetry, and blood pressure.

7.13.5. Eastern Cooperative Oncology Group Performance Status

The Investigator or qualified designee will assess ECOG performance status (Appendix G) at Screening and repeated as per the frequency defined in Appendix A1, Appendix A2, or Appendix B.

7.13.6. Adverse Event Monitoring

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the SOE (Appendix A1, Appendix A2, or Appendix B) and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (National Cancer Institute 2020; Section 8) and CRS and neurotoxicity per ASTCT criteria (Lee 2019; Appendix D).

Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to study treatment.

Refer to Section 8 for detailed information regarding the assessment and recording of AEs.

7.13.7. Disease Assessments

7.13.7.1. Monotherapy Disease Assessment During Study – Single Dose

In the monotherapy arms following Appendix A1, radiographic disease assessments will be performed pre-treatment, at Day 29±2 days for first scan, then Q8W±2W for Year 1 (i.e., Weeks 12, 20, 28, 36, 44, 52), then Q12W±2W for Year 2. There is a ± 2-day window for assessments performed after Day 1, and a ± 14-day window for assessments after Day 29.

7.13.7.2. Monotherapy Disease Assessment During Study – Two Doses

In the monotherapy arm following Appendix B, radiographic disease assessments will be performed pre-treatment, at Day X +28±2 days for first scan, then Q8W±2W for Year 1 after the second dose, then Q12W±2W for Year 2 after the second dose. There is a ± 2-day window for assessments performed after Day 1, and a ± 14-day window for assessments after Day 29.

7.13.7.3. Combination Therapy Disease Assessment During Study

In the combination arm following Appendix A2, radiographic disease assessments will be performed at Week 8 for the first scan to allow adequate time after the 1st pembrolizumab administration for clinical activity to develop, then Q8W±2W for Year 1 (i.e., Weeks 16, 24, 32, 40, and 48 [± 3 days]), then Q12W±2W for Year 2 (i.e., Weeks 60, 72, 84, and 96 [± 3 days]).

7.13.7.4. Disease Assessment of Immunotherapeutic Agents

Immunotherapeutic agents such as TAC01-HER2 may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. 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 response assessment criteria may not provide a CR assessment of immunotherapeutic agents. However, imaging should occur at any time where there is clinical suspicion of progression, and it should be confirmed by second set of scans 28 days after the Day 29 scans (± 14 days).

7.13.8. Assessment of Disease and Tumor Response

7.13.8.1. Disease Response Assessment

Disease assessments should be performed using CT (or MRI if indicated) scans at Baseline (Screening and/or after bridging anticancer therapy), and confirmation of CRs and PRs at the

next scheduled scan. Scans will be reviewed and assessed locally by the Investigator and radiology using RECIST 1.1.

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). 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.

The Investigator or qualified designee must review pre-study images to confirm the subject has measurable disease prior to LDC. Central laboratory review of scans may be requested by Triumvira. Response assessment is based on the immune responses assigned to RECIST 1.1 described in Appendix F.

An MRI may replace CT scans following discussion with the Medical Monitor. See the Imaging Manual for details.

7.13.8.2. Tumor and Correlative Studies Blood Collection

For Phase 1 and Phase 2:

In both phases, in addition to subjects who are HER2+ by central laboratory confirmation (i.e., IHC+ and FISH+), subjects who are HER2+ via recent (preferably after last line of therapy or within 1 year) local laboratory results using IHC, FISH, or next generation sequencing (NGS) assays may also be enrolled, as long as a recent (preferably fresh or archival within 1 year) tissue biopsy sample is available for central laboratory HER2+ confirmation after enrollment or starting TAC01-HER2. In the instance of discordant results between central and local laboratories (i.e., central laboratory results are negative with regards to IHC or FISH), the subject will still be considered evaluable for safety and evaluation of DLTs. In the instance of discordant results between central and local laboratories, the subject may be replaced in Phase 2.

Central laboratory confirmation of HER2+ tumor samples will occur by one of the following methods (in order of priority):

a. A fresh tumor tissue sample, if clinically feasible and safe
b. An archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1)
c. A liquid biopsy to examine circulating tumor cells
d. If a, b, or c are not obtainable, the most recent archival sample available regardless of when it was obtained during prior lines of therapy

Fine needle aspirations, or brushing and scraping cytology samples, are not acceptable at Baseline or Screening. Since Phase 2 will be evaluating efficacy and since HER2 status often changes on progression after HER2-targeted therapies (e.g., trastuzumab), it is strongly recommended a fresh tumor tissue sample be obtained, if clinically feasible and safe, along with

the corresponding pathology report for histological disease diagnosis confirming HER2-protein expression on the tumor cell surface.

ASCO/College of American Pathologists (CAP) guidelines will be followed for assessment of breast and gastric specimens. For all other tumor types, the assessment guidelines for breast cancer specimens will be followed.

Exploratory biopsies should be limited to percutaneous lesions that are palpable, or guided by imaging if necessary, and not be taken from any lesions that are in proximity to vital visceral, cardio-pulmonary, or neurovascular structures. When feasible biopsy sites should be selected so that subsequent biopsies can be performed at the same location. Tumors that are inaccessible or contraindicated due to subject's safety concerns are exempt from being biopsied.

For Phase 1, tumor biopsies on Days 11 and 29 post-TAC01-HER2 infusion and at disease progression are optional and should not preclude subjects from participating in the study. An FNA may be performed as an alternative to the Day 11 and Day 29 biopsies when appropriate.

For Phase 2, these biopsies are mandatory if clinical feasible and safe, unless discussed with, and waived by, the Medical Monitor. Subjects who refuse the post-treatment mandatory biopsy requirements will not be precluded from enrollment, nor discontinued from the study, and exceptions may be made after discussion with the Medical Monitor or designee on a case-by-case basis.

Tumor biopsies will be collected as per Table 11. These time points were updated from Amendment 4 (i.e., from pre-dose and Day 8) to screening and Days 11 and 29, to better evaluate the presence of TAC T cells in the tumor microenvironment, as recent nonclinical data indicate PK/PD effects are best evaluated 2-4 weeks post TAC01-HER2 dosing.

Table 11: Tumor Tissue Assessments

Type of Biopsy	Timing of Biopsy
Tumor Tissue	Screening, Day 11, Day 29, at disease progression, or as clinically indicated

In the monotherapy and combination therapy arms, blood for correlative biomarker studies should be collected as per Table 12 for subjects who receive a single dose and Table 13 for subjects who receive a second dose (monotherapy only).

Table 12: Monotherapy and Combination Therapy Blood Collection for Pharmacokinetic and Correlative Biomarkers Studies

Indication	Timing of Correlative Blood Collection
Whole blood for PK studies	Pre-LDC, Days 3, 4 or 5, 8, 11, 14/15[a], 18, 21/22[a], 25, 29, 42, Months 3, 6, 9, 12, 18, 24 or EOS, and at the confirmatory PD visit
Whole blood for biomarker studies	Pre-LDC, Days 8, 11, 14/15[a], 21/22[a], 29, 42, Months 3, 6, 9, 12, 18, 24 or EOS, and at the confirmatory PD visit
Serum for cytokine studies	Pre-LDC, Days 3, 4 or 5, 8, 11, 14/15[a], 18, 21/22[a], 25, 29, 42, Months 3, 6, 9, 12, 18, 24 or EOS, and at the confirmatory PD visit
Whole blood for RCL testing	Pre-LDC, Months 3, 6, 12, and 24

PD=progressive disease; PK=pharmacokinetics; RCL=replication-competent lentivirus
[a] Note: Day 15 and 22 correspond to monotherapy (see Appendix A1) and Day 14 and 21 correspond to combination therapy (see Appendix A2).

Table 13: Pharmacokinetic, Biomarker, Cytokine Blood Collection (After Second Dose)

Indication	Timing of Correlative Blood Collection
Whole blood for PK studies	Pre-LDC, Days X+2, X+3 or 4, X+7, X+10, X+14, X+17, X+21, X+24, X+28, X+41, Months 3, 6, 9, 12, 18, 24 or EOS
Whole blood for biomarker studies	Pre-LDC, Days X+7, X+10, X+14, X+21, X+28, X+41, Months 3, 6, 9, 12, 18, 24 or EOS
Serum for cytokine studies	Pre-LDC, Days X+2, X+3 or 4, X+7, X+10, X+14, X+17, X+21, X+24, X+28, X+41, Months 3, 6, 9, 12, 18, 24 or EOS

PD=progressive disease; PK=pharmacokinetics; RCL=replication-competent lentivirus

7.13.9. Laboratory Safety Evaluations

Screening and other laboratory evaluations (see Table 14) will be performed at study visits indicated in Appendix A1, Appendix A2, or Appendix B. Additional assessments should be performed between scheduled study visits as clinically required to diagnose and monitor AE or expected events. Requirements for reporting laboratory abnormalities are provided in Section 8.5.2.

Laboratory tests for hematology, chemistry, urinalysis, and other laboratory tests are specified in Table 14. Except for analyses of PK, biomarkers, or other prognostic indicators (proteomics, genetics, transcriptional analysis, antibodies), all tests will be conducted locally.

Table 14: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG) [a]
Hemoglobin	Alkaline phosphatase	Glucose	Prothrombin time (PT), International Normalized Ratio (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	Activated partial thromboplastin time (aPTT)
White blood cell count (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Fibrinogen
Red blood cell count	Bicarbonate	Microscopic examination if abnormal results are noted	C-reactive protein (CRP)
Absolute neutrophil count	Blood urea nitrogen		Ferritin
Absolute lymphocyte count	Calcium		Triglycerides
	Chloride		Human immunodeficiency virus (HIV) 1/2
	Creatinine		Hepatitis B, C
	Glucose		Immunoglobulin G (IgG)
	Lactate Dehydrogenase (LDH)		Triiodothyronine (T3) or free T3 (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH)
	Phosphorus		Central Laboratory Analysis:
	Potassium		Blood for PK
	Sodium		Blood for biomarkers
	Total Bilirubin		Blood for cytokines
	Direct Bilirubin if total bilirubin is elevated above the upper limit of normal		Blood for replication-competent lentivirus (RCL)
	Total protein		Tumor biopsy specimen for human epidermal growth factor 2 (HER2) status and biomarker analysis
	Uric acid		

[a] Perform on women of childbearing potential only.

7.13.10. Blood Collection for Human Anti-Mouse Antibodies

The human anti-mouse antibodies (HAMA) sample is part of the biomarker analysis. Sample collection, storage, and shipment instructions will be provided in the Laboratory Manual. Biomarker samples should be drawn according to the schedule in Appendix A1, Appendix A2, or Appendix B.

7.13.11. Future Biomedical Research

The following specimens are to be obtained as part of FBR:

Tumor including primary and potential metastatic sites and blood for genomics use:

- Unused tumor tissue biopsies
- Unused correlative blood samples
- Unused TAC01-HER2 product
- Unused leukapheresis product

7.13.12. Other Procedures

7.13.12.1. Central Laboratory Analysis Samples

Testing and analysis of samples will follow the SOE in Appendix A1, Appendix A2, or Appendix B. Allocation of samples to specific testing may be modified where sample material is limited; however, the total volume and type of material collected will not be modified beyond what is described in the Laboratory Manual.

Detailed information regarding the collection, handling, and shipment of samples for PK, cytokine, biomarker, and RCL assessments is provided in the Laboratory Manual.

7.13.12.2. Pharmacokinetic Assessments

Assessment of TAC T cell expansion and persistence in blood will be determined by quantitative polymerase chain reaction (qPCR) to detect the TAC-HER2 transgene and by flow cytometry to enumerate the number and immunophenotypic TAC T cells.

7.13.12.3. Cytokine Assessments

Assessment of various cytokine levels will be determined in serum samples by immunoassay.

7.13.12.4. Biomarker Assessments

Biomarker assessments will be performed to evaluate HER2+ tumor status, and immune system characteristics that may be associated with TAC01-HER2 toxicity, clinical activity, and resistance mechanisms to TAC01-HER2 treatment. See the Laboratory Manual for further details.

7.13.12.5. PD-L1 Expression Level Assessment

All subjects receiving pembrolizumab are required to have their tumors assessed for the level of PD-L1 expression at Baseline. Previously determined local results are acceptable. New biopsies and local analyses are required to be performed, if no other results or samples are available.

7.13.12.6. Replication Competent Lentivirus Assessment

RCL testing will be performed using an analytically validated polymerase chain reaction (PCR)-based assay to detect the viral envelope sequence in peripheral blood. If all samples collected within the first year after the final dose of TAC01-HER2 are negative, subsequent samples will be archived at a central laboratory. However, if any of the samples are positive, additional testing will be performed to confirm the result. If the repeat test is also positive, further analysis of the RCL will be undertaken to ascertain the nature of the RCL and potential effects such as vector integration with detailed sequencing and other relevant assays. PBMCs and deoxyribonucleic acid (DNA), processed according to validated laboratory procedures in a CAP/Clinical Laboratory Improvements Amendments (CLIA) licensed laboratory, will be archived at each specimen collection point for retrospective assessments if indicated.

Any confirmed positive result from RCL testing will be reported as an adverse event in the form of an Investigational New Drug (IND) safety report.

If a subject develops a new or recurrent neoplasm, Triumvira will request a sample of the neoplastic tissue for assessment of RCL.

7.14. Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.

7.14.1. Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for FBR and have their leftover specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the Investigator for the main study. If medical records for the main study are still available, the Investigator will contact Triumvira. Subsequently, the subject's specimens will be removed from the biorepository and destroyed. A notification will be sent from Triumvira to the Investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by Triumvira will continue to be used as part of the overall research study data and results. No new analyses will be generated after the request is received.

In the event that the medical records for the main study are no longer available (e.g., if the Investigator is no longer required by regulatory authorities to retain the main study records) or

the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

8. SAFETY MONITORING AND REPORTING

8.1. Overview

AEs will be assessed throughout the study according to CTCAE Version 5.0 (National Cancer Institute 2020), and CRS and neurotoxicity per ASTCT (Lee 2019) Consensus Criteria. AEs, SAEs, and laboratory abnormalities (type, frequency, and severity) will be collected. Potential TAC T cell related toxicities may include infusion reactions, CRS, neurotoxicity, macrophage activation syndrome, and TLS; with the list of these risks being updated during the study based on any observed safety signals. RCL and, if positive, follow-up viral vector sequence, testing will be performed at specified time points during the study using PCR-based assays.

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death. AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). See Section 8.5.4 for timeframes where death due to PD is considered an SAE. The Investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome.

All AEs or events of clinical interest (ECIs) from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.

8.2. Definitions

8.2.1. Adverse Event Definition

In accordance with ICH E2A guideline and United States (US) Code of Federal Regulation (CFR), Title 21 Part 312.32, an AE is defined as any untoward medical occurrence in a clinical study subject, administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, whether or not it is associated with an AE, should be reported on the Study Drug Administration CRF even if there is no reported injury. Any sequela of an overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, it must be reported on a SAE report form. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures, as necessary. There is no known specific antidote for TAC01-HER2, fludarabine/cyclophosphamide, clofarabine/cyclophosphamide, single agent cyclophosphamide or single agent bendamustine overdose. Actual treatment should depend on the severity of the clinical situation and the judgment of the treating physician.

8.2.2. Serious Adverse Event Definition

An SAE is defined as an event that, at any dose, meets any of the criteria in Table 15. Special considerations for SAE reporting, including events that should always be reported as SAEs in this study, are presented in Table 16.

Table 15: Definitions of SAEs

Criteria	Description
Fatal	The AE resulted in death.
Life-threatening	The AE placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might have caused death if it had been more severe.
Hospitalization/prolongation of hospitalization	The AE resulted in hospitalization or prolongation of hospitalization.
Disability/incapacity	The AE resulted in a disability, significant incapacity, or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly/birth defect	The AE was an adverse outcome in a child or fetus of a subject exposed to the study treatment regimen before conception or during pregnancy.
Medically important	The AE was a medically important event that did not meet any of the above criteria but may have jeopardized the subject and may have required medical or surgical intervention to prevent 1 of the outcomes listed above (examples include allergic bronchospasm that required treatment in an emergency room, seizures that do not result in hospitalization, or blood dyscrasias).

Table 16: Special Considerations for SAE Reporting

Criteria	Description
Events that should always be reported as SAEs	• New/secondary malignancies • New onset or exacerbation of a pre-existing neurologic disorder • New onset or exacerbation of rheumatologic or other autoimmune disorder • New onset hematologic disorder • Rare and unexpected disorders with an unknown etiology (e.g., Guillain-Barre, Stevens-Johnson's syndrome)
Hospitalization/prolongation of hospitalization Complications and/or prolonged admissions for routine treatment or procedure do require SAE reporting.	This classification **does not** apply to hospital admissions for the following reasons: • Social or situational reasons in the absence of any clinical AE. • At the Investigator's discretion for lymphodepleting chemotherapy or TAC01-HER2 administration. • Elective or pre-planned treatment or procedure for a pre-existing condition that is unrelated to the condition under study and has not worsened since providing informed consent. • Routine treatment (e.g., platelet transfusion) or monitoring of the condition under study that is not associated with any deterioration in condition. • Routine procedures (e.g., bone marrow aspiration) associated with the disease under study. • Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

8.2.3. Pembrolizumab Events of Clinical Interest

Selected non-serious AEs and SAEs are also known as ECIs and must be reported to Triumvira within 24 hours of awareness.

Pembrolizumab ECIs for this trial include:

1. An overdose of pembrolizumab (as defined in Section 5.5), that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT laboratory value that is ≥3 x ULN and an elevated total bilirubin laboratory value that is ≥2 x ULN and, at the same time, an alkaline phosphatase laboratory value that is <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.3. Grading and Intensity of Adverse Events

AEs will be graded using the NCI CTCAE Version 5.0 (National Cancer Institute 2020) and CRS and neurotoxicity per ASTCT (Lee 2019) criteria for CRS and neurotoxicity as outlined in Appendix D. The reported verbatim term should be the most descriptive medical diagnosis and does not have to be found in CTCAE.

8.4. Relationship to Investigational Product

The assessment of the relationship of an AE to the administration of the investigational product (related or not related) is a clinical decision based on all available information and the considerations listed in Table 17. There are 2 investigational products in this study: TAC01-HER2 and pembrolizumab.

Table 17: Assessment of Relationship for Adverse Events

Relationship	Considerations
Related	There is at least a reasonable possibility and/or evidence to suggest a causal relationship between investigational product and the AE/SAE and no other more likely alternative cause (concomitant drugs, therapies, disease complications, etc.) is suspected.
Not related	There is no reasonable possibility and/or evidence to suggest a causal relationship between investigational product and the AE/SAE and another more likely alternative cause (concomitant drugs or therapies, disease complications, etc.) is suspected.

8.5. Recording and Reporting of Adverse Events

AEs recorded on the CRF must be supported by documentation in the subject's study records.

AEs/SAEs recorded on the CRF will be evaluated for:

- Duration (onset and resolution dates)
- Outcome
- Seriousness (see Section 8.2.2)
- Severity (see Section 8.3)
- Causal relationship with TAC T cells (see Section 8.4)

8.5.1. Recording a Diagnosis versus Signs and Symptoms

Whenever possible, a unifying diagnosis should be reported as opposed to a listing of individual symptoms. However, symptoms should be grouped into a diagnosis only if each sign or symptom is a medically confirmed component of that diagnosis as evidenced by current standard medical literature. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE.

Two exceptions to reporting a diagnosis as opposed to symptoms are the events of CRS and neurotoxicity. If a subject experiences CRS and/or neurotoxicity, a diagnosis of CRS and/or neurotoxicity and any grade changes for the event should be reported as an AE. Individual signs and symptoms of CRS and/or neurotoxicity, and the maximum grade for those signs and symptoms, should be entered on the respective CRS and neurotoxicity

8.5.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Any laboratory abnormality (e.g., clinical chemistry or hematology) or other abnormal assessment findings (e.g., ECG or vital signs) that meets any of the following criteria should be recorded as an AE/SAE:

- Requires medical or surgical intervention
- Leads to product discontinuation, delay, or interruption
- Associated with clinical signs and/or symptoms
- Otherwise clinically significant as determined by the Investigator

Whenever possible, the clinical diagnosis, rather than the laboratory result, should be reported (e.g., anemia versus low hematocrit).

Clinically significant abnormal laboratory values occurring during the study will be evaluated, graded, and followed per the CTCAE v5.0 until repeat tests return to normal or baseline, stabilize, or are no longer clinically significant.

8.5.3. Recording Serious Adverse Events

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in death should be recorded on the CRF and reported on the SAE report form.
- For hospitalizations or surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.
- Events related to disease progression must be reported to Triumvira's Pharmacovigilance Team if they meet serious criteria. When reporting a disease progression SAE, specific manifestations of the progression (e.g., "new bone pain" or "worsening anemia and renal failure") should be reported, rather than the general term "disease progression."

Additionally, any SAE brought to the attention of an investigator at any time outside of the time periods specified above must be reported immediately to Triumvira if the event is considered to be drug related.

8.5.4. Death Reports

Deaths must be reported as an SAE on the Death CRF and to Triumvira's Pharmacovigilance Team per the reporting periods described in Table 18 and Table 19.

A death due to disease progression must be reported to Triumvira's Pharmacovigilance provider as an SAE if it occurs from the start of leukapheresis to within 90 days after TAC01-HER2 administration in the monotherapy arm, or up to 90 days after the last dose of pembrolizumab in the combination arm. Deaths that occur in the monotherapy arm more than 90 days after TAC01-HER2 infusion will be captured on the Death CRF and reported as an SAE only if considered related to any protocol mandated procedure and/or TAC T cells. Deaths that occur in the combination arm more than 90 days after the last pembrolizumab infusion will be captured on the Death CRF and reported as an SAE only if considered related to any protocol mandated procedure, TAC T cells, and/or pembrolizumab.

8.5.5. Pregnancy Reporting

Subjects will be instructed to continue using appropriate methods of contraception until 1 year after their last dose of TAC01-HER2 or 120 days after their last pembrolizumab dose or 30 days after their last pembrolizumab dose if the subject starts a new anticancer therapy, whichever is longer. If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated.

Any pregnancy that occurs in a female subject or the female partner of a male subject within 1 year after their last TAC01-HER dose, while on treatment with pembrolizumab, or within 120 days of their last pembrolizumab dose should be recorded on a Clinical Study Pregnancy Form and submitted to the Triumvira's Pharmacovigilance provider within 24 hours of awareness. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Deaths, and congenital anomalies/birth defects, as defined by the "seriousness criteria" in Section 8.2.2, should be reported as SAEs.

All pregnancies that occur within the timelines above should be monitored for the full duration, and all perinatal and neonatal outcomes should be reported without delay. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Triumvira.

In summary, all pregnancies and exposure during breastfeeding, from the time of treatment allocation through 1 year after their last TAC01-HER2 dose, 120 days after their last dose of pembrolizumab, or 30 days after their last dose of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

8.5.6. Use in Nursing Women

It is unknown whether 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, participants who are breastfeeding are not eligible for enrollment.

8.5.7. Adverse Event Reporting Periods

Reporting periods are summarized in Table 18 (AEs and SAEs) and Table 19 (AEs, ECIs, and SAEs).

SAEs will be followed until they resolve or return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator, the subject dies or withdraws consent, or the study is closed. All non-serious AEs will be followed through the safety reporting period described in Table 18 and Table 19. Certain non-serious AEs, as requested by Triumvira, may be followed until resolution, return to baseline, or study closure.

8.5.8. Serious Adverse Event Reporting

SAEs that are considered related to TAC01-HER2, pembrolizumab, or both must be reported to Triumvira within 24 hours of awareness. Clinical conditions listed in Section 8.2.2 must be reported within 24 hours of awareness regardless of relationship to the investigational product. The Investigator is required to send the completed SAE Form and any supporting documentation (e.g., hospital admission notes, test results) to Triumvira's Pharmacovigilance Team according to the instructions on the SAE report form. Within 24 hours of receipt of follow-up information, the Investigator must submit an updated SAE report and/or supporting documentation per the same procedure. SAEs must also be reported to the reviewing IRB/IEC per IRB/IEC requirements. A copy of any IRB/IEC submission must be retained and filed in the Investigator Site File.

For initial SAE reports, the following minimum criteria must be reported on the SAE form:

- Subject number
- Event onset date
- Event description
- Study treatment
- Relationship to study treatment

Table 18: Reporting Periods for AEs and SAEs in the Monotherapy Arm

Time Period	Events to Record
Informed consent to leukapheresis	AEs/SAEs related to protocol-mandated procedures
Leukapheresis to lymphodepleting chemotherapy start	AEs related to protocol-mandated procedures and all SAEs
From lymphodepleting chemotherapy start to 90 Days post-TAC01-HER2 dose (or 30 days post last lymphodepleting chemotherapy dose if discontinued before TAC01-HER2 administration)	All AEs/SAEs
Subjects starting a non-chemotherapeutic anticancer therapy prior to 90 days post-TAC01-HER2 dose	All AE/SAEs for 90 days following final TAC01-HER2 infusion or for 30 days following subsequent therapy, whichever is longer.
Subjects starting a chemotherapeutic anticancer therapy prior to 90 days post-TAC01-HER2 dose	After initiation of subsequent therapy, only AEs and SAEs related to TAC01-HER2 or a protocol-mandated procedure.
91 days Post-TAC01-HER2 dose to end of study (EOS)	Only AEs and SAEs related to TAC01-HER2 or a protocol-mandated procedure.

Table 19: Reporting Periods for AEs, ECIs, and SAEs in the Combination Arm

Time Period	Events to Record
Informed consent to leukapheresis	AEs/SAEs related to protocol-mandated procedures
Leukapheresis to lymphodepleting chemotherapy start	AEs related to protocol-mandated procedures and all SAEs
From lymphodepleting chemotherapy start to 90 days after the last pembrolizumab dose	All AEs/SAEs
Subjects starting a non-chemotherapeutic anticancer therapy prior to 90 days after the last pembrolizumab dose	All AE/SAEs for 90 days after the last pembrolizumab dose or for 30 days following subsequent therapy, whichever is longer.
Subjects starting a chemotherapeutic anticancer therapy prior to 90 days after the last pembrolizumab dose	After initiation of subsequent therapy, only AEs and SAEs related to pembrolizumab or TAC01-HER2 or a protocol-mandated procedure and all SAEs for 90 days after the last pembrolizumab dose or 30 days after the last pembrolizumab dose .if the subject initiates further anticancer therapy,
91 days after the last pembrolizumab dose to EOS	Only AEs and SAEs related to pembrolizumab or TAC01-HER2 or a protocol-mandated procedure.

Triumvira is responsible for reporting serious, unexpected AEs/experiences to the relevant competent regulatory authority.

The Investigator and Triumvira (or their delegated Medical Monitor) will determine whether expedited reporting is necessary for SAEs depending on their assessment of seriousness, expectedness, and relationship. IND/CTA Safety Reports will be implemented as appropriate and sent to the relevant competent regulatory authority within the regulatory timeframe appropriate for the outcome of their assessment.

8.5.8.1. Expedited Reporting

Any AE/experience that is unexpected and is assessed as serious and related to study treatment is subject to expedited reporting requirements (e.g., Suspected Unexpected Serious Adverse Reaction [SUSAR]).

In accordance with the CFR, Title 21 Part 312.32 and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting (E2A guideline), Triumvira must submit written documentation in the form of an IND/CTA Safety Report. Written

submission must be made to the relevant competent regulatory authority as soon as possible and no later than 15 calendar days after Triumvira's initial notification of the event/experience.

In addition, any unexpected fatal or life-threatening events associated with the use of the study product must be reported to the relevant competent regulatory authority by either telephone or facsimile transmission as soon as possible and no later than 7 calendar days after initial notification of the event/experience.

8.5.8.2. Non-Expedited Reporting

All SAEs that do not require expedited reporting will be submitted to the relevant competent regulatory authority in the annual development safety update reports to the INDs/CTAs.

8.6. Data Safety Monitoring Committee

A DSMC will be established prior to enrollment of the first subject. The DSMC will be responsible for reviewing safety on a regular basis and clinical activity data at the time of interim analysis. An introductory meeting will be held to describe the roles and responsibilities of the DSMC members and discuss potential data format and process issues and agree upon a charter.

Detailed description of the DSMC membership and meeting frequency will be outlined in the DSMC charter.

It is envisioned that the DSMC may make the following types of recommendations, namely:

At time of safety review:

- No safety issues, ethical to continue the study as planned;
- Serious safety concerns precluding further study treatment;
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments).

At time of interim analysis:

- No safety issues, ethical to continue the study as planned;
- Ethical to continue the study but recommend an amendment to the protocol (e.g., incorporate additional or more frequent safety examinations);
- Serious safety concerns precluding further study treatment;
- Insufficient evidence of clinical activity, not ethical to continue the study as planned.

DSMC recommendations will be provided in compliance with the DSMC charter.

9. STATISTICAL METHODS

9.1. Overview and Sample Sizes

In Phase 1, the keyboard dose escalation design (Appendix C) will govern the number of subjects to be enrolled. It is estimated 27 to 54 subjects may be enrolled, i.e., ~3-6 subjects for each of the 4 dose levels across 2 arms (monotherapy and combination therapy; Figure 9). Based on the cumulative data from subjects treated in the dose finding phase, the MTD or RP2D will be selected for further evaluation in the dose expansion portion of the study. Once identified, an additional 3-6 subjects may be treated at the RP2D to confirm safety before proceeding to Phase 2.

In Phase 2, up to 36 subjects will be enrolled in monotherapy **Group A** using a Simon 3 stage design assessing futility to show a maximum- ineffective ORR of 6.0% and a minimum effective ORR of 20%. If 0 subjects have a response among the first 11 subjects in the cohort, the study will be stopped for a lack of efficacy. If >0 subjects have a response, then another 14 subjects will be enrolled, for a total of 25 monotherapy subjects. If ≤2 of the 25 subjects have a response, the study will be stopped for lack of efficacy. If >2 subjects have a response, then another 11 subjects will be enrolled in the third stage, for a total of 36 monotherapy subjects. If ≤4 of the 36 subjects have a response, then treatment with TAC01-HER2 as a monotherapy will not be considered as having adequate efficacy to continue investigation in HER2+ subjects. If >4 of the 36 subjects have a response, then treatment with TAC01-HER2 as a monotherapy will be considered efficacious and continued clinical study investigations will be warranted. The assumed ORR was selected based on the results of the TAGS study for Trifluridine/tipiracil, which enrolled gastric cancer and GEJ AC subjects after 2 prior lines of therapy. Since the ORR in that study was 4% (Shitara 2018), it was considered that the assumed 20% ORRs for Group A is clinically meaningful.

In Phase 2, up to 34 subjects will be enrolled in combination therapy **Group B** using a Simon 3-stage design assessing futility to show a maximum ineffective ORR of 8.4% and a minimum effective ORR of 25%. If 0 subjects have a response among the first 9 subjects in the cohort, the study will be stopped for a lack of efficacy. If >0 subjects have a response, then another 10 subjects will be enrolled, for a total of 19 combination therapy subjects. If ≤2 of the 19 subjects have a response, the study will be stopped for lack of efficacy. If >2 subjects have a response then another 15 subjects will be enrolled in the third stage, for a total of 34 combination therapy subjects. If ≤5 of the 34 subjects have a response, then treatment with TAC01-HER2 in combination with pembrolizumab will not be considered as having adequate efficacy to continue investigation in HER2+ subjects. If >5 of the 34 subjects have a response, then treatment with TAC01-HER2 in combination with pembrolizumab will be considered efficacious and continued clinical study investigations will be warranted. The assumed clinically meaningful ORR for group B was also selected based on the results of the TAGS study for Trifluridine/tipiracil. Since the ORR in that study was 4% (Shitara 2018) and given the anticipated add on benefit for the combination it was considered that the assumed 25% ORRs for group B is clinically meaningful.

Simon Three-Stage Design Sample Size and Cutoff Requirements for Phase 2 (Dose Expansion)		
Parameter	Group A	Group B
Maximum non-effective rate	6.0%	8.4%
Minimum effective rate	20.0%	25.0%
First stage total N	11	9
First stage cutoff	0	0
Second stage total N	25	19
Second stage cutoff	2	2
Final stage total N	36	34
Final stage cutoff	4	5

All data from all available subjects (i.e., dose escalation and dose expansion phases) will be used when evaluating the potential efficacy of TAC01-HER2. Efficacy and safety of TAC01-HER2 will be determined both as a monotherapy and in combination with pembrolizumab. In addition, efficacy of TAC01-HER2 will be explored for subjects who received bridging therapy versus those who did not and subjects who received 1 dose of TAC01-HER2 versus those that received a second dose versus those who were eligible for a second dose but did not receive a second dose. In addition, safety will also be explored for subjects who received 1 dose versus those who received a second dose versus those who were eligible for a second dose but did not receive a second dose. Additional details and other subgroup analyses will be described in the Statistical Analysis Plan (SAP).

Subjects who are in DLT evaluation cohorts will be considered evaluable if they complete the defined DLT observation period. Estimates of ORR and other response proportions (e.g., DCR) will be presented together with 95% confidence intervals calculated using the Clopper-Pearson method. Kaplan-Meier estimations will be used for the analysis of time-to-event endpoints, including DOR, OS, and PFS.

The cellular kinetics of TAC01-HER2 will be determined from individual concentration-time profiles of circulating TAC T cells and characterized in peripheral blood and summarized by treatment arm.

9.2. General Considerations

All analyses will be separated by monotherapy and combination therapy treatment arms and dose levels, unless otherwise specified. In the Phase 1 portion of the study, summaries will be prepared by treatment arm, and summarized by dose level and overall. Data from Phase 1 at the RP2D and data from Phase 2 will be pooled for analysis. Analyses may be refined in a detailed statistical analysis plan following further discussion with regulatory authorities.

By-subject listings will be provided. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation,

95% CIs on the mean as appropriate, median, minimum, and maximum. Summary tables for categorical variables will include the following: N, n, percentage, and 95% CIs on the percentage as appropriate. Kaplan-Meier (KM) estimation will be used for the analysis of time to event endpoints, including DOR and OS.

For the efficacy analysis, the ITT population is defined as any subject that received at least 1 course of TAC01-HER2.

Subjects in the monotherapy arm who do not receive TAC01-HER2 will be included in by-subject listings but will not be included in data summaries unless otherwise specified.

Subjects in the combination therapy arm who receive TAC01-HER2 but not ≥1 dose of pembrolizumab will be included in the monotherapy arm.

Subjects who receive non-conforming product of TAC01-HER2 will be analyzed separately.

9.3. Analysis Sets

9.3.1. Analysis Sets for Phase 1

9.3.1.1. Screened Analysis Set

The screened analysis set includes all subjects who have signed informed consent.

9.3.1.2. Leukapheresis Analysis Set

The leukapheresis analysis set includes all subjects who have signed informed consent and who undergo leukapheresis.

9.3.1.3. Safety Analysis Set

The safety analysis set includes all subjects who receive TAC01-HER2.

9.3.1.4. Monotherapy Dose Limiting Toxicity-Evaluable Analysis Set

The monotherapy DLT-evaluable analysis set includes all subjects who have received TAC01-HER2 at the assigned dose level, and who have either experienced a DLT or were followed for the full DLT evaluation period. This analysis set will be used for the determination of the MTD or RP2D. The monotherapy DLT-evaluable period is defined as Days 1 through 28, for a total evaluation period of 28 days following TAC01-HER2 infusion, and up to 42 days should clinically consequential (i.e., events associated with febrile neutropenia, serious infections, or bleeding) Grade ≥3 neutropenia or thrombocytopenia occur.

9.3.1.5. Combination Therapy Dose Limiting Toxicity-Evaluable Analysis Set

The combination DLT-evaluable analysis set includes all subjects who have received TAC01-HER2 at the assigned dose level and ≥1 dose of pembrolizumab, and who have either

experienced a DLT or were followed for the full DLT evaluation period. This analysis set will be used for the determination of the MTD or RP2D.

The combination DLT-evaluable period is defined as Days 1 to 42 for subjects who receive pembrolizumab on Day 21 and Days 1 to 35 for subjects who receive pembrolizumab on Day 14.

9.3.1.6. Monotherapy Efficacy Analysis Set

The monotherapy efficacy analysis set in Phase 1 includes all subjects who have received TAC01-HER2, have measurable disease at the last disease assessment prior to receiving TAC01-HER2, and who have at least 1 post-infusion disease response assessment.

9.3.1.7. Combination Therapy Efficacy Analysis Set

The combination therapy efficacy analysis set in Phase 1 includes all subjects who have received TAC01-HER2, have measurable disease at the last disease assessment prior to receiving TAC01-HER2, received ≥1 dose of pembrolizumab, and who have at least 1 post-infusion disease response assessment following a pembrolizumab.

9.3.1.8. Pharmacokinetic Analysis Set

The PK analysis set includes subjects in the safety analysis set who have the necessary PK measurements to provide interpretable results for the specific parameters of interest.

9.3.2. Analysis Sets for Subjects Treated at the RP2D

9.3.2.1. Safety Analysis Set

The safety analysis set includes all subjects who receive TAC01-HER2 at the RP2D. This analysis set will be used in the analyses of safety endpoints.

9.3.2.2. Monotherapy Efficacy Analysis Set

The monotherapy efficacy analysis set includes all subjects across Phase 1 and Phase 2 of the study who have measurable disease at the last disease assessment prior to TAC01-HER2 infusion and who receive product at the RP2D. All efficacy endpoints will be analyzed using this analysis set.

9.3.2.3. Combination Therapy Efficacy Analysis Set

The combination therapy efficacy analysis set includes all subjects across Phase 1 and Phase 2 of the study who have measurable disease at the last disease assessment prior to TAC01-HER2 infusion and who receive TAC01-HER2 at the RP2D and receive ≥1 dose of pembrolizumab. All efficacy endpoints will be analyzed using this analysis set.

9.3.2.4. Additional Analysis Sets

The Phase 2 screened set, leukapheresis analysis set, and PK analysis set will follow the same definitions as in Phase 1. Additional analysis sets may be defined in the SAP.

9.4. Planned Analyses

9.4.1. Subject Disposition and Baseline Characteristics

Descriptive summaries of demographics, baseline characteristics, and subject disposition will be provided for each analysis set.

9.4.2. Primary Endpoints in Phase 1 Dose Escalation

The primary endpoints are:

- Incidence of DLTs
- The type and incidence of DLTs will be summarized by dose level and total. The rates of DLT at each dose level and the MTD will be estimated using isotonic regression as described in Yan, Mandrekar and Yuan (2017).
- Type, frequency, and severity of AEs

All AEs will be listed and summarized (see Section 8 for details).

9.4.3. Secondary Endpoints in Phase 1 Dose Escalation

Separate MTD or RP2D will be determined for the monotherapy and combination arm of the study. Additional secondary endpoints are:

- C_{max}, T_{max}, and AUC of TAC T cells.

Determination of these parameters will be based on data obtained after the TAC01-HER2 infusion through the Day 29 visit. C_{max} is the maximal concentration of TAC T cells (or peak cell expansion) after infusion. T_{max} is the first study day the C_{max} is reached. AUC will be calculated using the trapezoid rule.

Duration of persistence of TAC T cells: Persistence will be defined as the time between the first measurement of transgene above the limit of detection until the last observed quantifiable level of transgene (C_{last}).

ORR is defined as the percentage of treated subjects with a CR or PR; DOR is defined as time from first response to disease progression, end of study, start of another anticancer therapy, or death; OS is defined as time from infusion to death from any cause according to RECIST 1.1 as assessed by the Investigator; DCR is defined as the percentage of treated subjects with SD, PR, and CR; and PFS is defined as the time from infusion to disease progression or death from any

cause according to RECIST 1.1 as assessed by the Investigator. Subjects without any reported disease response assessments will be considered non responders.

In addition, immunogenicity to treatment will be assessed, as well as any correlations with PK and efficacy characteristics. Candidate efficacy biomarkers will also be investigated.

9.4.4. Primary Endpoints in Phase 2 Expansion

ORR will be calculated as the proportion of subjects with a best overall response of either CR or PR based on RECIST 1.1 (Schwartz 2016). Exact 95% confidence limits for ORR will be calculated using the Clopper-Pearson method. DCR will also be calculated taking into account stable disease, PR, and CR.

DOR will be defined as the time from the first date when measurement criteria are met for PR or CR (whichever status is recorded first) to the date that measurement criteria are first met for PD or the date of death, whichever is sooner. For subjects not known to have died as of the data cutoff date and who do not have PD, DOR will be censored at the last progression-free assessment date. For responding subjects who receive subsequent anticancer therapy prior to disease progression, DOR will be censored at the date of last progression-free assessment prior to the initiation of a new anticancer therapy.

OS will be calculated as the time from the date of TAC01-HER2 infusion to the date of death from any cause. For a subject who is still alive as of the data cut-off date, OS time will be censored on the subject's date of last contact.

PFS will be calculated as the time from the date of TAC01-HER2 infusion to the date of disease progression of from death from any cause. For a subject who is still alive as of the data cut-off date and has not been evaluated with PD, PFS time will be censored on the subject's date of last contact.

Time-to-event endpoints, including DOR, OS and PFS, will be summarized descriptively and graphically using KM methodology. KM estimates for the median, first, and third quartiles will be determined along with 95% CIs. The Brookmeyer-Crowley method will be used for the CI calculations. For the subset of subjects who have a CR or PR, DOR will be summarized similarly using the Kaplan-Meier method. TTR will be defined from TAC01-HER2 infusion to the first documented CR or PR and will be summarized descriptively as a continuous variable.

ORR and other efficacy endpoints will be examined within subgroups defined by the following factors:

- Age: <40 versus ≥40 years at the time of TAC01-HER2 infusion
- Level of HER 2 expression: 1+, 2+, 3+ (Phase 1) and 2+ and 3+ (Phase 2)
- PD-L1 expression for pembrolizumab treated subjects

- Subjects who received 1 TAC01-HER2 dose versus subjects who received a second TAC01-HER2 dose versus subjects who were eligible for a second TAC01-HER2 dose but did not receive it.
- Subjects who received anticancer bridging therapy versus subjects who did not receive bridging therapy.

9.4.5. Secondary Endpoints in Phase 2 Expansion

Secondary endpoints are:

- Type, frequency, and severity of AEs.

All AEs will be listed and summarized (see Section 8 for details).

Additional secondary endpoints are:

- C_{max}, T_{max}, and AUC of TAC T cells.

Determination of these parameters will be based on data obtained after the TAC01-HER2 infusion through the Day 29 visit. C_{max} is the maximal concentration of TAC T cells (or peak cell expansion) after infusion. T_{max} is the first study day the C_{max} is reached. AUC will be calculated using the trapezoid rule.

Duration of persistence of TAC T cells: Persistence will be defined as the time between the first measurement of transgene above the limit of detection until the last observed quantifiable level of transgene (C_{last}).

In addition, we will assess immunogenicity to treatment, as well as any correlations with PK and efficacy characteristics. We will also investigate candidate efficacy biomarkers.

9.4.6. Safety Analyses

Safety analyses will be based on the safety analysis set.

9.4.6.1. Adverse Events

All AEs will be listed. The focus of AE summarization will be on TEAEs.

In the monotherapy arm, a TEAE is defined as an AE that starts any time from initiation of TAC01-HER2 administration through and including 90 days following the TAC01-HER2 dose as well as any pre-existing AE that worsens after study treatment. Any AE occurring after the initiation of another anticancer treatment will not be considered a TEAE.

In the combination arm, a TEAE is defined as an AE that starts any time after initiation of TAC01-HER2 administration until 90 days after the last dose of pembrolizumab.

Once a subject starts a new anticancer therapy and transfers to the minimal study procedures in the LTFU protocol, TEAEs will no longer be collected.

Reporting of AEs will be based on the Medical Dictionary for Regulatory Activities (MedDRA), NCI CTCAE Version 5.0 (National Cancer Institute 2020) and CRS and neurotoxicity per ASTCT criteria (Lee 2019) as outlined in Appendix D. The incidence of TEAEs will be summarized by system organ class, preferred term, and severity. A subject who reports multiple occurrences of TEAEs within the same system organ class and preferred term is counted only once using the maximum severity grade for summaries.

9.4.6.2. Laboratory Data

All laboratory data will be listed. The focus of laboratory data summarization (including hematology and serum chemistry) will be on treatment-emergent laboratory abnormalities.

In the monotherapy arm, a treatment-emergent laboratory abnormality is defined as an abnormality when, compared to baseline, worsens by at least 1 grade within 90 days following the TAC01-HER2 infusion.

In the combination arm, a treatment-emergent laboratory abnormality is defined as an abnormality when, compared to baseline, worsens by at least 1 grade up to 90 days after the last dose of pembrolizumab.

The baseline value is defined as the last available recorded value on or prior to the date of the TAC01-HER2 infusion.

If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥1 in severity) will be considered treatment emergent. Hematological and serum biochemistry data will be graded according to NCI CTCAE Version 5.0 when applicable. Grade 0 includes all non-missing values that do not meet the criteria for an abnormality of at least Grade 1. Grade 5 will not be used. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

The following summaries will be presented for selected analytes:

- Raw values and changes from Baseline will be summarized by visit for numerical laboratory results in conventional units.
- Number of subjects by CTCAE, with corresponding percentages at each visit, and maximum post-Baseline severity grade.
- Number and percentage of subjects with a treatment emergent CTCAE Grade 3 or 4 laboratory abnormality.
- Shift tables showing the change in CTCAE severity grade from Baseline to the maximum severity grade post Baseline. For laboratory tests where CTCAE grade does not exist, the shift table will present the low/normal/high shift.

9.4.6.3. Other Safety Analyses

Vital signs will be summarized using descriptive statistics and listed. All other safety data will be listed.

9.4.6.4. Safety Subgroup Analyses

Safety summaries will be prepared for all subjects in the safety analysis set, and for subgroups based on:

- Age: <40 versus ≥40 years at the time of the TAC01-HER2 infusion
- Subjects who received 1 TAC01-HER2 dose versus subjects who received a second TAC01-HER2 dose versus subjects who were eligible for a second TAC01-HER2 dose but did not receive it.
- Subjects who received anticancer bridging therapy versus subjects who did not receive bridging therapy.

9.4.7. Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHO-DD) and listed. All concomitant medications and blood product transfusions administered after the TAC01-HER2 infusion will be summarized.

Specific treatments for CRS (e.g., corticosteroids, tocilizumab) will be summarized, as will specific treatments for neurotoxicity.

Anticancer interventions will be summarized.

9.4.8. Pharmacokinetic Analyses

Individual concentration-time profiles of circulating TAC T cells will be obtained from peripheral blood samples. Graphs of serum concentration curves will be prepared overall and for individual subjects.

9.4.8.1. Cellular Kinetic Parameters for TAC01-HER2

Parameters will be estimated by noncompartmental methods using Phoenix (Pharsight, Version 6.4). Derived parameters of interest will include AUC (0 – 29 days) and AUC (0 – 3 months) (reflecting expansion of the modified T cells following infusion of TAC01-HER2), C_{max}, and T_{max}. AUC will be calculated using the linear trapezoidal rule. C_{max} corresponds to the maximum (peak) expansion of TAC T cells, while T_{max} corresponds to the time at which this maximum expansion is observed. Conventional methods will be used to derive additional cellular kinetic parameters, such as C_{last} (the last observed quantifiable level of transgene), T_{last} (the level of transgene at the last quantifiable time point), and $T_{1/2}$. $T_{1/2}$ will be calculated as ln 2/λz, for which

λz (the apparent terminal elimination rate constant) is estimated by linear regression of the terminal log-linear portion of the concentration-time curve.

Summary statistics of cellular kinetic parameters from peripheral blood will be presented overall and by Day 29. Measures of persistence, including T_{last} and C_{last}, will be used as indicators of the duration that TAC T cells are present in peripheral blood and tissues.

PK parameters will be summarized using descriptive statistics for all subjects in the PK analysis set and for subgroups based on:

- Age: <40 versus ≥40 years at the time of the TAC01-HER2 infusion
- Cellular and/or humoral immunogenicity present (positive) or absent (negative)

9.4.9. Exploratory Endpoints

The exploratory endpoints for the study are listed in Table 4. Details of the exploratory analyses are provided in the SAP.

9.5. Timing of Analyses

9.5.1. Interim Analysis

In addition to assessing safety data for the occurrence of dose limiting toxicities, a Simon 3-stage design will be used to assess the futility of treatment with TAC01-HER2 among HER2+ gastric and esophageal adenocarcinoma subjects as monotherapy and in combination with pembrolizumab (see Section 9.1).

In Phase 2, up to 36 subjects will be enrolled in monotherapy **Group A** using a Simon 3 stage design assessing futility to show a maximum- ineffective ORR of 6.0% and a minimum effective ORR of 20%. If 0 subjects have a response among the first 11 subjects in the cohort, the study will be stopped for a lack of efficacy. If >0 subjects have a response, then another 14 subjects will be enrolled, for a total of 25 monotherapy subjects. If ≤2 of the 25 subjects have a response, the study will be stopped for lack of efficacy. If >2 subjects have a response, then another 11 subjects will be enrolled in the third stage, for a total of 36 monotherapy subjects. If ≤4 of the 36 subjects have a response, then treatment with TAC01-HER2 as a monotherapy will not be considered as having adequate efficacy to continue investigation in HER2+ subjects. If >4 of the 36 subjects have a response, then treatment with TAC01-HER2 as a monotherapy will be considered efficacious and continued clinical study investigations will be warranted. The assumed ORR was selected based on the results of the TAGS study for Trifluridine/tipiracil, which enrolled gastric cancer and GEJ AC subjects after 2 prior lines of therapy. Since the ORR in that study was 4% (Shitara 2018), it was considered that the assumed 20% ORRs for Group A is clinically meaningful.

In Phase 2, up to 34 subjects will be enrolled in combination therapy **Group B** using a Simon 3-stage design assessing futility to show a maximum ineffective ORR of 8.4% and a minimum effective ORR of 25%. If 0 subjects have a response among the first 9 subjects in the cohort, the

study will be stopped for a lack of efficacy. If >0 subjects have a response, then another 10 subjects will be enrolled, for a total of 19 combination therapy subjects. If ≤2 of the 19 subjects have a response, the study will be stopped for lack of efficacy. If >2 subjects have a response then another 15 subjects will be enrolled in the third stage, for a total of 34 combination therapy subjects. If ≤5 of the 34 subjects have a response, then treatment with TAC01-HER2 in combination with pembrolizumab will not be considered as having adequate efficacy to continue investigation in HER2+ subjects. If >5 of the 34 subjects have a response, then treatment with TAC01-HER2 in combination with pembrolizumab will be considered efficacious and continued clinical study investigations will be warranted. The assumed clinically meaningful ORR for group B was also selected based on the results of the TAGS study for Trifluridine/tipiracil. Since the ORR in that study was 4% (Shitara 2018), and given the anticipated add on benefit for the combination it was considered that the assumed 25% ORRs for group B is clinically meaningful.

9.5.2. Final Analysis

The final analyses will be carried out after all subjects have completed or discontinued the study for any reason. No formal hypothesis testing will be performed at the final analysis.

10. DATA MANAGEMENT

10.1. Data Collection System

An electronic data capture (EDC) system will be used for data collection. The EDC system will be a fully validated, secure system that conforms to 21 CFR Part 11 requirements. Access to the EDC system will be role-based, and login credentials will be provided only after completion of the assigned role-based training.

10.2. Data Quality

Investigative site personnel will enter data on the CRFs in the EDC system. A Monitor will verify data recorded on the CRFs is consistent with the source documents.

To ensure complete and accurate data, automated data validation checks programmed within the EDC system will flag missing and non-conformant data during data entry. Data review by the Triumvira project team may result in additional queries. All data entry and subsequent data changes and query resolutions are logged in an audit trail in the EDC system.

The Investigator is responsible for ensuring the data entered on the CRFs are complete and accurate and will electronically sign the CRFs attesting to this for each subject prior to database lock. Following database lock, an electronic copy of the final subject casebook will be provided to the investigative site for archival.

11. STUDY ADMINISTRATION

11.1. Regulatory and Ethical Compliance

The study will be conducted in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), the protocol, and any other applicable national, state, and/or local regulatory requirements (e.g., US CFR Title 21, and World Medical Association Declaration of Helsinki).

11.2. Regulatory Authority Review

Before initiation of this study, the protocol must be reviewed and approved by the appropriate competent regulatory authorities.

11.3. Institutional Review Board/Independent Ethics Committee Approval

It is the Investigator's responsibility to ensure the appropriate IRB/IEC or equivalent local committee has reviewed and approved this protocol prior to study initiation. The IRB/IEC or equivalent local committee must also review and approve the investigative site's ICF and all applicable subject materials.

If the protocol or ICF are amended during the study the Investigator is responsible for ensuring the IRB/IEC or equivalent local committee has reviewed and approved these amended documents. IRB/IEC or equivalent local committee approval of the amended documents must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF.

11.4. Subject Informed Consent

The Investigator, or a qualified designee, will be responsible for explaining the nature, purpose, benefits, and risks of participation in the study to each subject, subject's legally acceptable representative, or impartial witness. Written informed consent must be obtained before the initiation of any study specific procedure. Sufficient time must be allowed to discuss any questions raised by the subject. The Investigator or qualified designee will document this process in the study records. The Investigator must use the current IRB/IEC or equivalent local committee approved consent form for documenting written informed consent. The subject or the subject's legally authorized representative must appropriately sign and date each consent form. Signatures required by local policies (e.g., the person obtaining consent) must also be complete. Informed consent must be obtained in compliance with all national regulations, GCP/ICH requirements, and local laws.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The investigative site must use the amended ICF for all new subjects. If required by the IRB/IEC, the investigative site must also repeat the consent process with the amended ICF for any subject already enrolled in the study.

11.5. Investigator Responsibilities

The Investigator is responsible for ensuring all investigative site personnel conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP.

The Investigator will also ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998, or local regulatory guidelines for the country of location.

The Investigator and all study staff will comply with 21 CFR, Part 54, 1998, providing documentation of any financial conflict of interest. This documentation must be provided prior to the Investigator or Sub-Investigators' participation in the study. The Investigator and Sub-Investigator(s) agree to notify Triumvira of any change in reportable interests during the study and for 1 year following completion of the study at the investigative site.

If an amendment to either the protocol or study ICF is necessary, the Investigator will be responsible for ensuring the IRB/IEC or equivalent local committee reviews and approves the amended documents, and that subjects are informed of applicable changes and updates.

The Investigator will sign and return to Triumvira or designee the Protocol Signature Page for all pertinent versions of the protocol and will provide current medical licenses, curriculum vitae, and other forms requested by Triumvira. All forms must be updated as applicable throughout the study.

In accordance with applicable regulatory requirements, the Investigator is solely responsible for informing the IRB/IEC or equivalent local committee of study progress and notifying the IRB/IEC or equivalent local committee of study closure. The Investigator must also provide Triumvira or designee with copies of all IRB/IEC or equivalent local committee correspondence related to study approvals, renewals, updates, or changes.

11.6. Access to Information for Monitoring

In accordance with regulations and guidelines, the Monitor or designee must have direct access to the Investigator's source documentation to verify the accuracy of the data recorded on the CRF.

The Monitor or designee is responsible for routine review of the study records and CRFs at regular intervals throughout the study to verify adherence to GCP and protocol and the completeness, consistency, and accuracy of the data. The Investigator must agree to cooperate with the Monitor or designee to ensure any problems detected are resolved.

11.7. Quality Assurance

Triumvira or their designee may perform quality assurance checks of this study. Before the first subject enrollment, Triumvira or designee personnel will provide training to the Investigator, Sub-Investigators, and investigative site personnel regarding the informed consent process,

protocol, IB, CRF completion, and SAE reporting. Investigative site visits will be performed by Monitors or designees periodically throughout the study. During these site visits, information recorded on the CRFs may be verified against source documents, and requests for clarification or correction may be made. The CRFs will be reviewed for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. Requests for clarification or correction will be sent to Investigators via data queries.

11.8. Public Notification of Study Conduct

In compliance with Section 113 of the Food and Drug Modernization Act of 1997 and with publication requirements of the International Committee of Medical Journal Editors, Triumvira will be responsible for ensuring this study is listed on the ClinicalTrials.gov website per the US FDA requirement as well as on local study registries as required by health authorities and that information on the website relating to study design and conduct is appropriately updated during the study.

11.9. Study Termination

Upon completion or early termination of the study, the Investigator will return all study data (electronic and non-electronic) to Triumvira (the Investigator will be provided with a copy of the CRF data for their site), complete all data clarifications and/or resolutions, and allow a final Monitor review of study records for completeness.

11.10. Investigative Site Termination

Triumvira may terminate an Investigator's participation at any time for any reason. Termination and any required follow-up will be performed in compliance with 21 CFR Parts 312.50 and 312.56 and any applicable local regulations.

11.11. Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified in compliance with ICH GCP E6. Subject records, source documents, monitoring visit logs, regulatory documents, and correspondence pertaining to the study must be maintained at the investigative site. Source documents include but are not limited to all recordings, observations, or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. This includes any electronic records. Study records will be retained in a secure file for the period required by the institution or investigative site policy. Prior to the transfer or destruction of study records, Triumvira must be notified in writing and be given the opportunity to further store such records. Records are required to be retained as per applicable local laws, regulations, and/or guidelines.

11.12. Confidentiality

Subjects' names will remain confidential and will not be included in the study database. All study data and findings will be stored in electronic databases. The Investigator will maintain a subject ID list to ensure records can be linked to a specific subject.

11.13. Publication Plan

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to study execution may also be considered to determine authorship, provided that contributions have also been made to all 3 of the preceding authorship criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

Triumvira must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study at least 30 days prior to submission for publication/presentation. Any information identified by Triumvira as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Triumvira review can be expedited to meet publication timelines.

12. REFERENCES

Abramson JS, Palomba ML, Gordon LI, et al. High CR rin relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001). J Clin Oncol. 2017;35(15_suppl):7513.

Adusumilli PS, Zauderer MG, Rivière I, et al. A Phase I trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab. Cancer Discov. 2021;11:2748-63.

Barrett DM, Teachey DT, Grupp SA. Toxicity management for patients receiving novel T-cell engaging therapies. Curr Opin Pediatr. 2014;26:43-9.

Blank C, Brown I, Peterson AC, et al., PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res, 2004;64:1140-5.

Botta GP, Becerra CR, Jin Z et al. Multicenter phase Ib trial in the U.S. of salvage CT041 CLDN18.2-specific chimeric antigen receptor T-cell therapy for patients with advanced gastric and pancreatic adenocarcinoma. J Clin Oncol. 2022;40(16_suppl):2538.

Catenacci DVT, Kang YK, Park H, et al. Margetuximab plus pembrolizumab in patients with previously treated, HER2-positive gastro-oesophageal adenocarcinoma (CP-MGAH22-05): a single-arm, phase 1b-2 trial. Lancet Oncol. 2020;21:1066-76.

Chakrabarty A, Bhola NE, Sutton C, et al. Trastuzumab-resistant cells rely on a HER2-PI3K-FoxO-survivin axis and are sensitive to PI3K inhibitors. Cancer Res. 2013;73:1190-200.

Chemnitz JM, Parry RV, Nichols KE, et al. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol.2004;173:945–54.

Chmielecki J, Ross JS, Wang K, et al. Oncogenic alterations in ERBB2/HER2 represent potential therapeutic targets across tumors from diverse anatomic sites of origin. The Oncologist. 2015;20:7-12.

Chong EA, Alanio C, Svoboda J, et al. Pembrolizumab for B-cell lymphomas relapsing after or refractory to CD19-directed CAR T-cell therapy. Blood. 2022;139:1026-38.

Couzin J. Gene therapy. As Gelsinger case ends, gene therapy suffers another blow. Science. 2005;307:1028b.

Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A, 2010;107:4275-80.

Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6:224ra225.

De Gassart A, Le KS, Brune P, et al. Development of ICT01, a first-in-class, anti-BTN3A antibody for activating Vγ9Vδ2 T cell-mediated antitumor immune response. Sci Transl Med. 2021;13:eabj0835.

Deguchi Y, Okabe H, Oshima N, et al. PTEN loss is associated with a poor response to trastuzumab in HER2-overexpressing gastroesophageal adenocarcinoma. Gastric Cancer. 2017;20:416-27.

Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28:4531-8.

Donahue RE, Kessler SW, Bodine D, et al. Helper virus induced T cell lymphoma in nonhuman primates after retroviral mediated gene transfer. J Exp Med. 1992;176:1125-35.

Dudley ME, Wunderlich JE, Yang, JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol. 2005;23:2346-57.

Fodstad O, Aamdal S, McMenamin M, et al. A new experimental metastasis model in athymic nude mice, the human malignant melanoma LOX. Int J Cancer. 1988;41:442-9.

Fogh J, Fogh JM, Orfeo T. One hundred and twenty-seven cultured human tumor cell lines producing tumors in nude mice. J Natl Cancer Inst. 1977;59:221-6.

Food and Drug Administration. Draft Guidance for Industry: Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products. U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research; March 2022.

Food and Drug Administration. Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products. U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research; 2020.

Food and Drug Administration. Guidance for Industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up. U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research; 2020.

Francisco LM, Sage PT, and Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev.2010;219-42.

Gardner RA, Finney O, Smithers H, et al. Prolonged functional persistence of CD19CAR t cell products of defined CD4:CD8 composition and transgene expression determines durability of MRD-negative ALL remission. J Clin Oncol. 2016;35(15_suppl):3048.

Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018-28.

Gazdar AF, Kurvari V, Virmani A, et al. Characterization of paired tumor and non-tumor cell lines established from patients with breast cancer. Int J Cancer. 1998;78:766-74.

Greenwald RJ, Freeman GJ, and Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2005; 23:515–48.

Grossman Z, Min B, Meier-Schellersheim M, et al. Concomitant regulation of T-cell activation and homeostasis. Nat Rev Immunol. 2004;4:387-95.

Grosser R, Cherkassky L, Chintala N, et al. Combination immunotherapy with CAR T cells and checkpoint blockade for the treatment of solid tumors. Cancer Cell. 2019;36:471-82.

Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science. 2003;302:415-9.

Heczey A, Louis CU, Savoldo B, et al. CAR T Cells Administered in Combination with Lymphodepletion and PD-1 Inhibition to Patients with Neuroblastoma. Mol Ther. 2017;25:2214-24.

Helsen CW, Hammill JA, Lau VWC, et al. The chimeric TAC receptor co-opts the T cell receptor yielding robust anti-tumor activity without toxicity. Nat Commun. 2018;9:3049.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515:563-7.

Hirano F, Kaneko K, Tamura H, et al., Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65): 1089-96.

Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358:2698-703.

Ikediobi ON, Davies H, Bignell G, et al. Mutation analysis of 24 known cancer genes in the NCI-60 cell line set. Mol Cancer Ther. 2006;5:2606-12.

June CH, O'Connor RS, Kawalekar OU, et al. CAR T cell immunotherapy for human cancer. Science. 2018;359:1361-5.

Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol. 2015;33:540-9.

Lasfargues EY, Coutinho WG, Redfield ES. Isolation of two human tumor epithelial cell lines from solid breast carcinomas. J Natl Cancer Inst. 1978;61:967-78.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625-38.

Lewis GD, Figari I, Fendly B, et al. Differential responses of human tumor cell lines to anti-p185HER2 monoclonal antibodies. Cancer Immunol Immunother. 1993;37:255-63.

Li Z, Düllmann J, Schiedlmeier B, et al. Murine leukemia induced by retroviral gene marking. Science. 2002;296:497-497.

Lieber M, Mazzetta J, Nelson-Rees W, et al. Establishment of a continuous tumor-cell line (panc-1) from a human carcinoma of the exocrine pancreas. Int J Cancer. 1975;15:741-7.

Long AH, Haso WM, Shern JF, et al. 4-1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. Nat Med. 2015;21:581-90.

Maude S, Barrett DM. Current status of chimeric antigen receptor therapy for haematological malignancies. Br J Haematol. 2016;172:11-22.

Maude SL, Barrett D, Teachey DT, et al. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014a;20:119-22.

Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. New Eng J Med. 2014b;371:1507-17.

McGarrity GJ, Hoyah G, Winemiller A, et al. Patient monitoring and follow-up in lentiviral clinical trials. J Gene Med. 2013;15:78-82.

Miliotou AN, Papadopoulou LC. CAR T-cell Therapy: A New Era in Cancer Immunotherapy. Curr Pharm Biotechnol. 2018;19:5-18.

Modi S, Park H, Murthy RK, et al. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients with HER2-Low-Expressing Advanced Breast Cancer: Results from a Phase Ib Study. J Clin Oncol. 2020;38:1887-96.

Modi S, Jacot W, Yamashita T, et al. Trastuzumab din previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387:9-20.

Modlich U, Kustikova OS, Schmidt M, et al. Leukemias following retroviral transfer of multidrug resistance 1 (MDR1) are driven by combinatorial insertional mutagenesis. Blood. 2005;105:4235-46.

Morotti M, Albukhari A, Alsaadi A, et al. Promises and challenges of adoptive T-cell therapies for solid tumors. Br J Cancer. 2021 May;124:1759-76.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. In: U.S. Dept. of Health and Human Services, National Institutes of Health, National Cancer Institute; 2020.

Neelapu SS. CAR-T efficacy: is conditioning the key? Blood. 2019;133:1799-800.

Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. In. Vol 15: Nature Publishing Group; 2018:47-62.

Nomi T, Sho M, Akahori T, et al., Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13: p. 2151-7.

O'Donnell JS, Teng MWL, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. Nat Rev Clin Oncol. 2019;16:151-67.

Oh DY, Bang YJ. HER2-targeted therapies - a role beyond breast cancer. Nat Rev Clin Oncol. 2020;17:33-48.

Okazaki T, Maeda A, Nishimura H, et al. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98:13866-71.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Osborne W, Marzolini M, Tholouli E, et al. Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR T cell therapy, with pembrolizumab in patients with relapsed/refractory (r/r) DLBCL. J Clin Oncol. 2020;38:15_suppl, 8001.

Park JG, Frucht H, LaRocca RV, et al. Characteristics of cell lines established from human gastric carcinoma. Cancer Res. 1990;50:2773-80.

Parry RV, Chemnitz JM, Frauwirth KA., et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol, 2005;25:9543-53.

Pilon-Thomas S, Mackay A, Vohra N, et al., Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol 2010;184:3442-9.

Pinthus JH, Waks T, Malina V, et al. Adoptive immunotherapy of prostate cancer bone lesions using redirected effector lymphocytes. J Clin Invest. 2004;114:1774-81.

Qi C, Gong J, Li J, et al. Claudin 18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. Nat Met 2022;28:1189-98.

Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009; 229:114-25.

Rockett JC, Larkin K, Darnton SJ, et al. Five newly established oesophageal carcinoma cell lines: phenotypic and immunological characterization. Br J Cancer. 1997;75:258-63.

Rothe M, Modlich U, Schambach A. Biosafety challenges for use of lentiviral vectors in gene therapy. Curr Gene Ther. 2014;13:453-68.

Scholler J, Brady TL, Binder-Scholl G, et al. Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. Sci Transl Med. 2012;4:132ra153.

Schram A, Won HH, Andre F, et al. Abstract LB-103: Landscape of somatic ERBB2 Mutations: Findings from AACR GENIE and comparison to ongoing ERBB2 mutant basket study. Cancer Res. 2017;77(13_suppl):LB-103.

Schwartz LH, Litiere S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer. 2016;62:132-137.

Sheppard K-A, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett 2004;574:37-41.

Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomized, double-blind, placebo-controlled, phase 3 trial. Lance Oncol 2018;19:1437-48.

Spranger S, Koblish HK, Horton B, et al., Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer, 2014;2:3.

Spranger S, Spaapen RM, Zha Y, et al. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med. 2013;5:200ra116.

Stachel D, Futterer A, Haas RJ, Schmid I. Enhanced lymphocyte proliferation responses in pediatric patients early after myelosuppressive chemotherapy. Pediatr Blood Cancer. 2004;43:644-50.

Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 2003;63: 6501-5.

TCR^2 Therapeutics (28 Sep 2022). Gavo-cell continues to demonstrate clinical benefit in solid tumors with additional RECIST responses in ovarian cancer and mesothelioma (Press Release) GlobNewWire by Notified. Available from: https://www.globenewswire.com/en/search/organization/TCR2%2520Therapeutics

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-54.

Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515:568-71.

Turk MJ, Guevara-Patiño JA, Rizzuto GA, et al. Concomitant tumor immunity to a poorly immunogenic melanoma is prevented by regulatory T cells. J Exp Med. 2004;200:771-82.

Turtle CJ, Hanafi L-A, Berger C, et al. Rate of durable complete response in ALL, NHL, and CLL after immunotherapy with optimized lymphodepletion and defined composition CD19 CAR-T cells. J Clin Oncol. 2016;34(15_suppl):102-102.

Vafaei S, Zekiy AO, Khanamir RA, et al. Combination therapy with immune checkpoint inhibitors (ICIs); a new frontier. Cancer Cell Int. 2022;22:2.

Walsh N, Kennedy S, Larkin A, et al. EGFR and HER2 inhibition in pancreatic cancer. Invest New Drugs. 2013;31:558-66.

Wang GP, Levine BL, Binder GK, et al. Analysis of lentiviral vector integration in HIV+ study subjects receiving autologous infusions of gene modified CD4+ T cells. Molecular therapy: the journal of the American Society of Gene Therapy. 2009;17:844-50.

Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer-nonclinical background: CTLA-4 and PD-1 blockade. Semin Oncol. 2010;37:430-9.

World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013:310:2191-4.

Yan F, Mandrekar, SJ and Yuan Y. Keyboard: A novel bayesian toxicity probability interval design for Phase I clinical trials. Clinical Cancer Research 2017;23: 3994-4003.

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. In. Vol 2: Nat Rev Mol Cell Biol; 2001:127-37.

Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nature Med. 2017;23:703-13.

Zhang X, Schwartz J-C D, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20:337-47.

13. APPENDICES

APPENDIX A1. MONOTHERAPY SCHEDULE OF EVENTS (SUBJECTS WHO RECEIVE ONE DOSE)

Visit Schedule [a], Days, unless specified	Pre-Treatment				Treatment												Post-Treatment Follow-up[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	Lympho-depletion	Day 1	Day 2	Day 3	Day 4 or 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 42	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Window Days, unless specified			≤14 Prior to LDC		-4 to -2 Prior to Infusion[e]				+1	±1	±1	±2	±2	±2	±2	±2	±2	±14	±14	±14	±14	±14	±14	4 wk after initial PD
Administrative Procedures																								
Informed Consent	X																							
Informed Consent for Future Biomedical Research	X																							
Eligibility Criteria[s]	X		X			X																		
Subject Identification Card	X																							
Subject Identification Number	X																							
Demographics & Medical History	X																							
Prior & Concomitant Medication Review	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments																								
Leukapheresis		X																						
Optional Bridging Treatment [q]				X																				
Lymphodepleting					X																			

Visit Schedule [a], Days, unless specified	Pre-Treatment				Treatment													Post-Treatment Follow-up[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	Lympho-depletion	Day 1	Day 2	Day 3	Day 4 or 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 42	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Window Days, unless specified			≤14 Prior to LDC		-4 to -2 Prior to Infusion[e]				+1	±1	±1	±2	±2	±2	±2	±2	±2	±14	±14	±14	±14	±14	±14	4 wk after initial PD
Chemotherapy (LDC)																								
TAC01-HER2 Administration[f]						X																		
Physical Examination[i]	X		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
ECOG Performance Status	X		X		X[g]											X	X		X		X		X	X
Height	X																							
Weight	X				X[g]																		X	X
Vital Signs	X	X[n]	X		X	X[o]	X	X	X	X	X	X		X		X	X							
12-lead ECG	**X**																							
ECHO/MUGA Scan	X		X[b]																					
CT[p]	X		X[h]													At Day 29±2 days for first scan, then Q8W±2W for Year 1 (i.e., Weeks 12, 20, 28, 36, 44, 52), then Q12W±2W for Year 2. If at any time, a scan indicates a CR or PR, a confirmation scan should occur at the next scheduled scan.								X
Disease Response Assessment	X		X[h]																					X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Laboratory Procedures: analysis performed by local laboratory																								
Viral Serology	X																							
Serum Pregnancy Test	X[c]		X																				X	X

Visit Schedule [a], Days, unless specified	Pre-Treatment				Treatment													Post-Treatment Follow-up[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	Lympho-depletion	Day 1	Day 2	Day 3	Day 4 or 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 42	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Window Days, unless specified			≤14 Prior to LDC		-4 to -2 Prior to Infusion[e]				+1	±1	±1	±2	±2	±2	±2	±2	±2	±14	±14	±14	±14	±14	±14	4 wk after initial PD
Hematology	X	X[d]	X		X	X[j]	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	
Coagulation	X	X[d]	X		X	X[j]	X	X	X	X	X	X		X		X	X							
Serum Chemistry	X	X[d]	X		X	X[j]	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
CRP, Ferritin & Triglycerides			X			X[j]	X	X	X	X	X	X		X		X	X							
IgG levels			X						X			X				X	X	X	X	X	X	X	X	
Urine analysis			X													X	X	X	X	X	X	X	X	X
Laboratory Procedures: analysis performed by central laboratory																								
Fresh Tumor Biopsy	X[l]										X[k]					X[k]								X
PK Blood Sample			X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cytokine Blood Sample			X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker Blood Sample			X							X	X	X		X		X	X	X	X	X	X	X	X	X
RCL Blood Sample			X															X	X		X		X[m]	
HAMA	X															X								

Abbreviations: CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; IgG=immunoglobulin G; LDC=lymphodepleting chemotherapy; MUGA=multiple-gated acquisition; PD=progressive disease; PK=pharmacokinetics; RCL=replication-competent lentivirus.

[a] Assessments are scheduled relative to the subject's Triumvira TAC01-HER2 dose.

[b] Only required for subjects who receive potential cardiotoxic drugs as bridging therapy. Must be conducted within 7 days prior to lymphodepletion.

[c] Must be done at Screening and within 48 hours prior to initiating LDC.

[d] May be done up to 24 hours prior to leukapheresis.
[e] All evaluations should be performed daily prior to LDC administration unless otherwise indicated. Ideally, following LDC completion, after a 48-hour (± 24 hours) window, TAC01-HER2 should be infused. A window up to 5 days is acceptable between completion of LDC and TAC01-HER2 infusion.
[f] All evaluations should be performed prior to TAC01-HER2 administration unless otherwise indicated. TAC01-HER2 administration is described in Section 7.3.2. Premedication is summarized in 5.3.3.First day of lymphodepletion only.
[g] If a subject received bridging therapy, measurable disease needs to be confirmed prior to LDC.
[h] Physical examination can be performed by non-study personnel operating within their license.
[i] Must be collected prior to receiving TAC01-HER2 treatment.
[j] For Phase 1, optional post-treatment tumor biopsies (in subjects with accessible disease where it is clinically safe) will be obtained at 11 ± 1 day and 29 ± 2 days following the TAC01-HER2 dose. A fine needle aspiration (FNA) may be performed as an alternative when a fresh surgical or core needle biopsy is not clinically feasible. For Phase 2, the post-treatment biopsies are mandatory on Days 11 ± 1 and 29 ± 2 (as long as it is clinically feasible and safe). Subjects who refuse the post-treatment mandatory biopsy requirements will not be precluded from enrollment, nor discontinued from the study, and exceptions may be made after discussion with the Medical Monitor on a case-by-case basis.
[k] If a fresh biopsy is not feasible, then an archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1). If this is not feasible, a liquid biopsy to examine circulating tumor cells should be performed. Lastly, if this is not feasible, the most recent archival sample available regardless of when it was obtained during prior lines of therapy is acceptable.
[l] If prior RCL testing is negative, sample will be archived and analyzed as needed.
[m] Vital signs should be assessed prior to leukapheresis. Vital signs may be monitored during and after the procedure as clinically indicated.
[n] Vitals signs should be assessed approximately 15 minutes (± 5 min) prior to the TAC01-HER2 infusion, approximately every 15 minutes (± 5 min) after the infusion for the first hour, and approximately hourly (± 15 min) for the next 3 hours. After 4 hours post-infusion, vital signs should be monitored until stable and as clinically indicated.
[o] CT scans are requested at every imaging time point, unless MRI is used. The same imaging technique, methodology, and preferably the same equipment should be used on a subject throughout the study
[p] Bridging therapy is optional. Duration of bridging therapy is limited to a maximum of 4 weeks. All therapies must be discontinued at least 14 days prior to initiation of lymphodepletion and the time from leukapheresis to lymphodepletion cannot exceed 8 weeks ± 1 week.
[q] Post-Treatment Follow-Up begins on Day 43. If a subject has confirmed PD (i.e., with a confirmatory scan 28 days [± 7 days] after an initial scan indicating PD), or starts a new anticancer therapy, or the subject is unwilling or unable to continue the procedures, the subject will transition to the LTFU protocol.
[r] Eligibility checklists are to be submitted at least 24 hours before leukapheresis, LDC, and first infusion.

APPENDIX A2. COMBINATION THERAPY SCHEDULE OF EVENTS

	Pre-Treatment				Treatment														During or Post Pembro-Treatment[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	LDC	TAC01-HER2 on Day 1 only						Pembro Cycle 1					Cycles 2 to End (Q3W)	Cycle 2 Day 42 only	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Schedule [a], Days, unless specified (Pembrolizumab Cycle Days)			≤14 to LDC	≤4 weeks	-4 to -2 [e]	**1**	**2**	**3**	**4** or **5**	**8**	**11**	**14/ 21** (1)	**18/ 25** (5)	**21/ 28** (8)	**25/ 32** (12)	**29/ 36** (16)	**35/ 41** (1)	**42/ 49** (8)							4 wk after initial PD
Visit Window, Days, unless specified									+1	±1	±1	±2		±2		±2	±2 [t]	±2	±14	±14	±14	±14	±14	±14	±7
Administrative Procedures																									
Informed Consent	X																								
Informed Consent for Future Biomedical Research	X																								
Eligibility Criteria[w]	X		X			X																			
Subject Identification Card	X																								
Subject Identification Number	X																								
Demographics, Medical History, Baseline Symptoms	X																								
Prior & Concomitant Medication Review	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments																									
Leukapheresis		X																							
Bridging Treatment [q]				X																					
Lymphodepleting Chemotherapy (LDC)					X																				
TAC01-HER2 Admin. [f]						X																			

	Pre-Treatment				Treatment														During or Post Pembro-Treatment[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	LDC	TAC01-HER2 on Day 1 only			Pembro Cycle 1							Cycles 2 to End (Q3W)	Cycle 2 Day 42 only	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Schedule [a], Days, unless specified (Pembrolizumab Cycle Days)			≤14 to LDC	≤4 weeks	-4 to -2 [e]	**1**	**2**	**3**	**4** or **5**	**8**	**11**	**14/ 21** (1)	**18/ 25** (5)	**21/ 28** (8)	**25/ 32** (12)	**29/ 36** (16)	**35/ 41** (1)	**42/ 49** (8)							4 wk after initial PD
Visit Window, Days, unless specified									+1	±1	±1	±2		±2		±2	±2 [t]	±2	±14	±14	±14	±14	±14	±14	±7
Pembrolizumab Admin [f] Day 21 or Day 14 [v], then Q3W												X [v]		X [v]			X								
Physical Examination [i]	X		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X		X		X [g]							X					X	X							X
Height	X																								
Weight	X				X [g]							X					X								X
Vital Signs	X	X[n]	X		X	X [o]	X	X	X	X	X	X		X		X	X	X								
12-lead ECG	X											X													X
ECHO/MUGA Scan	X		X [b]																						
CT [p]	X		X [h]			At Week 8±2W for the first scan, then Q8W±2W for Year 1 (i.e., Week 16, 24, 32, 40, 48 [± 3 days]), then Q12W±2W for Year 2 (i.e., Week 60, 72, 84, 96 [± 3 days]) from TAC01-HER2 dose. If at any time, a scan indicates a CR or PR, a confirmation scan should occur at the next scheduled scan.																		X
Disease response assessments	X		X [h]																						X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
PD-L1 Expression Level	X [s]																								
Local Laboratory Procedures																									
Viral Serology	X																								

	Pre-Treatment				Treatment													During or Post Pembro-Treatment[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	LDC	TAC01-HER2 on Day 1 only			Pembro Cycle 1							Cycles 2 to End (Q3W)	Cycle 2 Day 42 only	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Schedule [a], Days, unless specified (Pembrolizumab Cycle Days)			≤14 to LDC	≤4 weeks	-4 to -2 [e]	**1**	**2**	**3**	**4** or **5**	**8**	**11**	**14/ 21** (1)	**18/ 25** (5)	**21/ 28** (8)	**25/ 32** (12)	**29/ 36** (16)	**35/ 41** (1)	**42/ 49** (8)							4 wk after initial PD
Visit Window, Days, unless specified									+1	±1	±1	±2		±2		±2	±2 [t]	±2	±14	±14	±14	±14	±14	±14	±7
Serum Pregnancy Test	X [c]		X																						X
Hematology	X	X [d]	X		X	X[j]	X	X	X	X	X	X [u]		X		X	X	X	X	X	X	X	X	X	X
Coagulation	X	X [d]	X		X	X[j]	X	X	X	X	X	X [u]						X							X
Serum Chemistry	X	X [d]	X		X	X[j]	X	X	X	X	X	X [u]		X		X	X	X	X	X	X	X	X	X	X
Thyroid Function Tests																		X	Every 6 weeks (T3 or FT3, FT4, TSH)						
CRP, Ferritin & Triglycerides			X			X[j]	X	X	X	X	X	X [u]						X							X
IgG levels			X						X			X [u]					X	X	X	X	X	X	X	X	X
Urine analysis			X									X [u]					X	X	X	X	X	X	X	X	X
Central Laboratory Procedures																									
Fresh Tumor Biopsy	X [l]										X [k]					X[k]									X
PK Blood Sample			X					X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Cytokine Blood Sample			X					X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Biomarker Blood Sample			X							X	X	X		X		X		X	X	X	X	X	X	X	X
RCL Blood Sample			X																X	X		X		X	X[m]

	Pre-Treatment				Treatment													During or Post Pembro-Treatment[r]						PD Visit[r]
	Screening	Leukapheresis	Pre-LDC	Bridging [q]	LDC	TAC01-HER2 on Day 1 only			Pembro Cycle 1							Cycles 2 to End (Q3W)	Cycle 2 Day 42 only	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS	
Visit Schedule [a], Days, unless specified (Pembrolizumab Cycle Days)			≤14 to LDC	≤4 weeks	-4 to -2 [e]	**1**	**2**	**3**	**4** or **5**	**8**	**11**	**14/ 21** (1)	**18/ 25** (5)	**21/ 28** (8)	**25/ 32** (12)	**29/ 36** (16)	**35/ 41** (1)	**42/ 49** (8)							4 wk after initial PD
Visit Window, Days, unless specified									+1	±1	±1	±2		±2		±2	±2 [t]	±2	±14	±14	±14	±14	±14	±14	±7
Blood for ctDNA	X																								X
HAMA			X													X									

Abbreviations: CRP=C-reactive protein; CT=computed tomography; ctDNA=circulating tumor DNA; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; FT3=free triiodo thyronine; FT4=free thyroxine; IgG=immunoglobulin G; LDC=lymphodepletion chemotherapy; MUGA=multiple-gated acquisition; PD=progressive disease; PK=pharmacokinetics; RCL=replication-competent lentivirus; T3=triiodothyronine; TSH=thyroid stimulating hormone.

[a] Assessments are first scheduled relative to the subject's TAC01-HER2 dose; however, after the first pembrolizumab dose, visits are scheduled based on pembrolizumab cycle days, but scans are always relative to the TAC02-HER2 dose on Day 1.

[b] Only required for subjects who receive potential cardiotoxic drugs as bridging therapy. Must be conducted within 7 days prior to lymphodepletion.

[c] Must be done at Screening and within 48 hours prior to initiating LDC.

[d] May be done up to 24 hours prior to leukapheresis.

[e] All evaluations should be performed daily prior to LDC administration unless otherwise indicated. Ideally, following LDC completion, after a 48-hour (± 24 hours) window, TAC01-HER2 should be infused. A window up to 5 days is acceptable between completion of LDC and TAC01-HER2 infusion.

[f] All evaluations should be performed prior to TAC01-HER2 administration or pembrolizumab administration, unless otherwise indicated. TAC01-HER2 administration is described in Section 7.3.2. Premedication is summarized in 5.3.3.

[g] First day of lymphodepletion only.

[h] If a subject received bridging therapy, measurable disease needs to be confirmed prior to LDC.

[i] Physical examination can be performed by non-study personnel operating within their license.

[j] Must be collected prior to receiving TAC01-HER2 treatment.

[k] For Phase 1, optional post-treatment tumor biopsies (in subjects with accessible disease where it is clinically safe) will be obtained approximately 11 ± 1 day and 29 ± 2 days following the TAC01-HER2 dose. A fine needle aspiration (FNA) may be performed as an alternative when a fresh surgical or core needle biopsy is not clinically feasible. For Phase 2, the post-treatment biopsies are mandatory on Days 11 ± 1 and 29 ± 2 (as long as it is clinically feasible and safe). Subjects who refuse the post-treatment mandatory biopsy requirements will not be precluded from enrollment, nor discontinued from the study, and exceptions may be made after discussion with the Medical Monitor on a case-by-case basis.

[l] If a fresh biopsy is not feasible, then an archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1). If this is not feasible, a liquid biopsy to examine circulating tumor cells should be performed. Lastly, if this is not feasible, the most recent archival sample available regardless of when it was obtained during prior lines of therapy is acceptable.

[m] If prior RCL testing is negative, sample will be archived and analyzed as needed.

[n] Vital signs should be assessed prior to leukapheresis. Vital signs may be monitored during and after the procedure as clinically indicated.

[o] Vitals signs should be assessed approximately 15 minutes (± 5 min) prior to the TAC01-HER2 infusion, approximately every 15 minutes (± 5 min) after the infusion for the first hour, and approximately hourly (± 15 min) for the next 3 hours. After 4 hours post-infusion, vital signs should be monitored until stable and as clinically indicated

[p] CT scans are requested at every imaging time point, unless MRI is used. The same imaging technique, methodology, and preferably the same equipment should be used on a subject throughout the study.

[q] Bridging therapy is optional. Duration of bridging therapy is limited to a maximum of 4 weeks. All therapies must be discontinued at least 14 days prior to initiation of lymphodepletion and the time from leukapheresis to lymphodepletion cannot exceed 8 weeks ± 1 week.

[r] Post-Treatment Follow-Up begins on Day 43. If a subject has confirmed PD (i.e., with a confirmatory scan 28 days [± 7 days] after an initial scan indicating PD), or starts a new anticancer therapy, or the subject is unwilling or unable to continue the procedures, the subject will transition to the LTFU protocol.

[s] All subjects receiving pembrolizumab are required to have their tumors assessed for the level of PD-L1 expression at Baseline. Previously determined local results are acceptable. New biopsies and local analyses are required to be performed, if no other results or samples are available.

[t] If the scheduled pembrolizumab dose occurs outside of the ± 2-day visit window, the subsequent pembrolizumab dose should be based on the actual date of the previous dose (i.e., Q3W ± 2 days from the previous dose).

[u] Laboratory tests should be taken prior to pembrolizumab infusion.

[v] Pembrolizumab administration will either begin on Day 14 **OR** Day 21 (i.e., at the Day 22 [± 2 days] visit), then occur Q3W for up to 2 years. Only a single dose should be administered either on Day 14 **OR** Day 21 as the start of pembrolizumab therapy. For additional details, see Section 3.2.

[w] Eligibility checklists are to be submitted at least 24 hours before leukapheresis, LDC, and first infusion.

APPENDIX B. MONOTHERAPY SCHEDULE OF EVENTS (SUBJECTS WHO RECEIVE 2 DOSES [ON DAY 1 AND DAY X])

Visit Schedule [a], Days unless specified	Pre-Treatment				Treatment													Post-Treatment Follow-up[r] Based on Day 1					
	Screening	Leukapheresis	Pre-LDC	Bridging [b]	Lympho-depletion	Day 1	Day 2	Day 3	Day 4 or 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 42	Day X Can occur any time after Day 29 (2nd dose)	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS
Visit Window Days, unless specified			≤14 Prior to LDC		-4 to -2 Prior to Infusion[c]				+1	±1	±1	±2	±2	±2	±2	±2	±2	2-3 weeks after criteria are met	±14	±14	±14	±14	±14	±14
Informed Consent	X																							
Informed Consent for Future Biomedical Research	X																							
Eligibility Criteria[s]	X		X			X																		
Subject Identification Card	X																							
Subject Identification Number	X																							
Demographics/Medical History	X																							
Prior and Concomitant Medication Review	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Leukapheresis		X																						
Optional Bridging Treatment[b]				X																				
Lymphodepleting Chemotherapy (LDC)					X													Day X-4 to X-2, as appropriate						

Visit Schedule [a], Days unless specified	Pre-Treatment				Treatment													Post-Treatment Follow-up[r] Based on Day 1					
	Screening	Leukapheresis	Pre-LDC	Bridging [b]	Lympho-depletion	Day 1	Day 2	Day 3	Day 4 or 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 42	Day X Can occur any time after Day 29 (2nd dose)	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS
Visit Window Days, unless specified			≤14 Prior to LDC		-4 to -2 Prior to Infusion[c]				+1	±1	±1	±2	±2	±2	±2	±2	±2	2-3 weeks after criteria are met	±14	±14	±14	±14	±14	±14
TAC01-HER2 Administration [d]						X												X						
Physical Examination [e]	X		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
ECOG Performance Status	X		X		X[f]											X	X	X		X		X		X
Height	X																							
Weight	X				X[f]													X	X	X	X	X	X	X
Vital Signs	X	X[g]	X		X	X[h]	X	X	X	X	X	X		X		X	X	X						
12-lead ECG	X																							
ECHO/MUGA Scan	X		X[i]																					
CT [j]	X		X[k]													Scans follow Phase 1 SOE until Day X		Day X +28, then Q8W (±2W) in Year 1, Q12W (±2W) in Year 2. If CR or PR, confirmation occurs at next scheduled scan						
Disease Response Assessment	X		X[k]																					
Adverse Events	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X
Viral Serology	X																							
Serum Pregnancy Test	X[l]		X																					X
Hematology	X	X[m]	X		X	X[p]	X	X	X	X	X	X		X		X	X	X, X+4, X+7, X+14, X+28	X	X	X	X	X	X

Visit Schedule [a], Days unless specified	Pre-Treatment				Treatment													Post-Treatment Follow-up[r] Based on Day 1					
	Screening	Leukapheresis	Pre-LDC	Bridging [b]	Lympho-depletion	Day 1	Day 2	Day 3	Day 4 or 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 42	Day X Can occur any time after Day 29 (2nd dose)	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24 or EOS
Visit Window Days, unless specified			≤14 Prior to LDC		-4 to -2 Prior to Infusion[c]				+1	±1	±1	±2	±2	±2	±2	±2	±2	2-3 weeks after criteria are met	±14	±14	±14	±14	±14	±14
Coagulation	X	X[m]	X		X	X[p]	X	X	X	X	X	X		X		X	X	X, X+4, X+7, X+14, X+28						
Serum Chemistry	X	X[m]	X		X	X[p]	X	X	X	X	X	X		X		X	X	X, X+4, X+7, X+14, X+28	X	X	X	X	X	X
CRP, Ferritin, and Triglycerides			X			X[p]	X	X	X	X	X	X		X		X	X	X, X+4, X+7, X+14, X+28						
IgG levels			X						X			X				X	X	X, X+4, X+7, X+14, X+28	X	X	X	X	X	X
Urinalysis			X													X	X	X, X+4, X+7, X+14, X+28	X	X	X	X	X	X
Fresh Tumor Biopsy	X[n]										X[o]					X[o]								
PK Blood Sample			X					X	X	X	X	X	X	X	X	X	X	Days X+2, X+3 or 4, X+7, X+10, X+14, X+17, X+21, X+24, X+28, X+41	X	X	X	X	X	X
Cytokine Blood Sample			X					X	X	X	X	X	X	X	X	X	X	Days X+2, X+3 or 4, X+7, X+10, X+14, X+17, X+21, X+24, X+28, X+41	X	X	X	X	X	X
Biomarker Blood Sample			X							X	X	X		X		X	X	Days X+7, X+10, X+14, X+21, X+28, X+41	X	X	X	X	X	X
RCL Blood Sample			X																X	X		X		X[q]
HAMA			X													X		X+28						

Abbreviations: CR=complete response; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; IgG=immunoglobulin G; LDC=lymphodepleting chemotherapy; MUGA=multigated acquisition; nab=nanoparticle albumin-bound; PD=progressive disease; PK=pharmacokinetics; PR=partial response; RCL=replication-competent lentivirus.

[a] Assessments are scheduled relative to the subject's TAC01-HER2 dose.

[b] Duration of bridging anticancer therapy is limited to a maximum of 4 weeks. All therapies must be discontinued at least 14 days prior to initiation of LDC. If the time from leukapheresis to the first LDC exceeds 8 weeks ± 1 week, subjects must be rescreened.

[c] All evaluations should be performed daily prior to LDC.

[d] All evaluations should be performed prior to TAC01-HER2 administration unless otherwise indicated. TAC01-HER2 administration is described in Section 7.3.2. Premedication is summarized in 5.3.3.

[e] Physical examination can be performed by non-study personnel operating within their license.

[f] First day of LDC only.

[g] Vital signs should be assessed prior to leukapheresis. Vital signs may be monitored during and after the procedure as clinically indicated.

[h] Vitals signs should be assessed approximately 15 minutes (± 5 min) prior to TAC01-HER2 administration, approximately every 15 minutes (± 5 min) after the infusion for the first hour, and approximately hourly (± 15 min) for the next 3 hours. After 4 hours post-infusion, vital signs should be monitored until stable and as clinically indicated.

[i] Only required for subjects who receive potential cardiotoxic drugs as bridging anticancer therapy. Must be conducted within 7 days prior to LDC.

[j] CT scans are required at every imaging time point, unless MRI is used. The same imaging technique, methodology, and preferably the same equipment should be used for a subject throughout the study.

[k] If a subject received bridging anticancer therapy, measurable disease needs to be confirmed prior to LDC.

[l] Must be done at Screening and within 48 hours prior to initiating LDC.

[m] May be done up to 24 hours prior to leukapheresis.

[n] If a fresh biopsy is not feasible, then an archival sample collected within 1 year prior to enrollment (samples may be collected >1 year prior to enrollment in Phase 1). If this is not feasible, a liquid biopsy to examine circulating tumor cells should be performed. Lastly, if this is not feasible, the most recent archival sample available regardless of when it was obtained during prior lines of therapy is acceptable.

[o] Optional for Phase 1, mandatory for Phase 2 (see Section 7.13.8).

[p] Must be collected prior to TAC01-HER2 administration.

[q] If prior RCL testing is negative, sample will be archived and analyzed as needed.

[r] Post Treatment Follow Up begins on Day 43.

[s] Eligibility checklists are to be submitted at least 24 hours before leukapheresis, LDC, and first infusion.

APPENDIX C. DOSE ESCALATION & DE-ESCALATION GUIDELINE

Keyboard Decision Table (Dose Finding)

Number of Subjects Treated at the Current Dose Level																				
Number of DLTs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0			E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1			S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		D	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
3			X	X	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E
4				X	X	X	D	D	D	D	D	S	S	S	S	S	E	E	E	E
5					X	X	X	X	X	D	D	D	D	D	S	S	S	S	S	S
6						X	X	X	X	X	X	D	D	D	D	D	D	S	S	S
7							X	X	X	X	X	X	X	D	D	D	D	D	D	D
8								X	X	X	X	X	X	X	X	X	D	D	D	D
9									X	X	X	X	X	X	X	X	X	X	X	D
10										X	X	X	X	X	X	X	X	X	X	X
11											X	X	X	X	X	X	X	X	X	X
12												X	X	X	X	X	X	X	X	X

N=20, P_{target}=0.30, ε1=0.05 and ε2= 0.05

The table will be applied separately for each dose level. Column indicates number of subjects treated within a given dose level; row indicates number of subjects with DLTs at that dose level.

E=Escalate to the next higher dose

S=Stay at the same dose

D=De-escalate to the previous lower dose

X=De-escalate to the previous lower dose and eliminate the current dose from further use in the study

After all subjects have been evaluated for DLT, the MTD will be selected based on isotonic regression as specified in Yan, Mandrekar and Yuan (Yan 2017). Specifically, the MTD is selected as the dose level with the isotonic estimate closest to the target DLT rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Note: Once the MTD is determined, up to 50 additional subjects will receive TAC01-HER2 at the RP2D. For subject safety, the dose elimination rule in the table above will be used as a stopping boundary for toxicity monitoring. With this rule, enrollment would be terminated if observed data indicate more than a 95% chance that the DLT rate is above the toxicity target (30%).

Operating Characteristics:

Table 20 shows the operating characteristics of the study design based on 1000 simulations of the study using shiny app "Keyboard" available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more subjects to the dose levels with the DLT rate closest to the target of 0.30.

Table 20: Operating Characteristics of the Keyboard Design

	Dose Level -1	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Number of Subjects	% Early Stopping
Scenario 1							
True DLT rate	0.30	0.47	0.53	0.58	0.64		
Selection %	58.2	19.3	5.7	1.6	0.4		14.8
# Pts treated	9.35	5.62	2.26	0.91	0.35	18.5	
Scenario 2							
True DLT rate	0.11	0.30	0.45	0.56	0.67		
Selection %	19.3	53.8	21.5	5	0.2		0.2
# Pts treated	4.33	8.5	4.7	1.87	0.57	20	
Scenario 3							
True DLT rate	0.02	0.07	0.13	0.30	0.47		
Selection %	0.1	1.7	23	55.4	19.8		0
# Pts treated	0.25	2.1	5.06	7.62	4.96	20	
Scenario 4							
True DLT rate	0.05	0.08	0.12	0.15	0.30		
Selection %	0.1	1.4	5.7	24.8	68		0
# Pts treated	0.29	1.98	2.62	5.09	10.02	20	

Note: "% Early Stopping" refers to early stopping due to excessive DLT.

APPENDIX D. CYTOKINE RELEASE SYNDROME AND NEUROTOXICITY GRADING

Cytokine Release Syndrome (CRS) Grading		
Grade	**Toxicity ASTCT Consensus Grading[b]**	
Grade 1	**Parameter**	
	Fever	Temperature greater than or equal to 38°C.
	With Hypotension	None.
	And/or Hypoxia	None.
Grade 2	**Parameter**	
	Fever	Temperature greater than or equal to 38°C.
	With Hypotension	Does not require vasopressors.
	And/or Hypoxia	Requires low-flow nasal cannula (less than 6L/min via nasal prongs).
Grade 3	**Parameter**	
	Fever	Temperature greater than or equal to 38°C.
	With Hypotension	Requires a vasopressor (with or without vasopressin).
	And/or Hypoxia	Requires high-flow nasal cannula (more than 6L/min via nasal prongs), facemask.
Grade 4	**Parameter**	
	Fever	Temperature greater than or equal to 38°C.
	With Hypotension	Requires multiple vasopressors (excluding vasopressin).
	And/or Hypoxia	Requires positive pressure (Continuous positive airway pressure [CPAP], BiPAP, intubation and mechanical ventilation).

a. b Adapted From: Lee 2019. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood and Marrow Transplantation. https://www.bbmt.org/article/S1083-8791(18)31691-4/fulltext5

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) Grading[a]				
Parameter:	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
ICE Score[b] (See Form)	Score 7-9	Score 3-6	Score 0-2	Score 0 (subject unarousable/unable to perform ICE).
Depressed Level of Consciousness	Awakens spontaneously.	Awakens to voice.	Awakens only to tactile stimulation.	Unarousable; requires vigorous tactile stimulation to rouse; stupor or coma.
Seizure	N/A	N/A	Any clinical seizure (focal or generalized) that rapidly resolves or non-convulsive on electroencephalogram (EEG) that resolves with intervention	Life-threatening prolonged seizure (over 5 minutes) or repetitive clinical or electrical seizures without return to baseline between.
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemi- or paraparesis.
Elevated ICP/ Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging.	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or Papilledema; or Cushing's Triad.

a. Adapted From: Lee 2019. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood and Marrow Transplantation. https://www.bbmt.org/article/S1083-8791(18)31691-4/fulltext5

b. The assessment can be performed by non-study personnel operating within their license.

APPENDIX E. ASSESSMENT AND MANAGEMENT CONSIDERATIONS CRS, NEUROTOXICITY AND MAS/HLH

Three Step Approach to Assessing and Managing TAC T cell Toxicity

Adapted from Neelapu 2018.

These are management recommendations for subjects who experience CRS, neurotoxicity, and/or MAS/HLH after TAC T cells.

Step 1: Monitor the subject's clinical and biological symptoms to determine the nature of the TAC T cell related toxicity, in order to diagnose CRS, neurotoxicity, and MAS/HLH.

Step 2: Grade the severity of CRS, neurotoxicity, and MAS/HLH using the criteria provided in Appendix D, Appendix E, and the NCI CTCAE Version 5.0, respectively.

Step 3: Treat the toxicities according to the management algorithms provided for CRS (Appendix D), neurotoxicity (Appendix E), and MAS/HLH (Appendix E).

Determining TAC T Cell Toxicity	CRS	Neurotoxicity	MAS/HLH

Step 1	• Fever
	• Hypotension
	• Hypoxia
	• Organ Toxicity
	  ○ Cardiac
	  ○ Respiratory
	  ○ Gastrointestinal
	  ○ Hepatic
	  ○ Renal
	  ○ Dermatological
	  ○ Coagulopathy
		• Orientation/Alertness
		  ○ Name Objects
		  ○ Writing
		  ○ Counting
		• Seizures
		  ○ Convulsive
		  ○ Non-convulsive
		• Increased ICP
		  ○ CSF Opening Pressure
		  ○ Papilloedema
		  ○ Cerebral Edema
		• Motor Weakness
			• Ferritin Level
			• Hepatic Toxicity
			• Renal Toxicity
			• Pulmonary Toxicity
			• Hemophagocytosis

Step 2	Grade CRS	Grade Neurotoxicity	Grade Organ Toxicity per NCI CTCAE Version 5.0
Step 3	Manage According to CRS Grade	Manage According to Neurotoxicity Grade	Manage as per Algorithm.

Cytokine Release Syndrome (CRS) Management

Grading refers to Lee 2019.

Adapted from Neelapu 2018.

CRS Grade	Symptom or Sign	Management
Grade 1	Fever or Organ Toxicity	• Acetaminophen and hypothermia blanket for fever. • Ibuprofen can be used as second treatment option for fever, if not contraindicated. • Assess for infection using blood and urine cultures, and chest radiography. • Empiric broad-spectrum antibiotics and filgrastim[a] if neutropenic. • Maintenance IV fluids for hydration. • Symptomatic management of constitutional symptoms and organ toxicities. • Consider tocilizumab[b] 8 mg/kg IV for persistent (lasting >3 days) and refractory fever.
Grade 2	Hypotension	• IV fluid bolus of 500–1,000 ml of normal saline • Can administer a second IV fluid bolus if systolic blood pressure (SBP) remains <90 mmHg • Tocilizumab[b] 8 mg/kg IV for the treatment of hypotension that is refractory to fluid boluses; tocilizumab can be repeated after 8 hours if needed. • If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain echocardiogram (ECHO), and initiate other methods of hemodynamic monitoring. • In subjects at high-risk[c] or if hypotension persists after 1–2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hours. • Manage fever and constitutional symptoms as in Grade 1.
	Hypoxia	• Supplemental oxygen. • Tocilizumab[b] with or without corticosteroids and supportive care, as recommended for the management of hypotension.
	Organ Toxicity	• Symptomatic management of organ toxicities, as per standard guidelines. • Tocilizumab[b] with or without corticosteroids and supportive care, as indicated for hypotension.

CRS Grade	Symptom or Sign	Management
Grade 3	Hypotension	• IV fluid boluses as needed, as recommended for the treatment of Grade 2 CRS. • If not administered previously, tocilizumab[b] as recommended for Grade 2 CRS. • Vasopressors as needed. • Transfer to ICU, obtain ECHO, and perform hemodynamic monitoring as in the management of Grade 2 CRS. • Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours. • Manage fever and constitutional symptoms as indicated for Grade 1 CRS.
	Hypoxia	• Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation. • Tocilizumab[b] plus corticosteroids and supportive care, as described above.
	Organ Toxicity	• Symptomatic management of organ toxicities as per standard guidelines. • Tocilizumab[b] plus corticosteroids and supportive care, as described above.
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as defined for the management of Grade 3 CRS. • Methylprednisolone 1 g/day IV. • Manage fever and constitutional symptoms as in Grade 1 CRS.
	Hypoxia	• Mechanical ventilation. • Tocilizumab[b] plus corticosteroids and supportive care, as described above.
	Organ Toxicity	• Symptomatic management of organ toxicities as per standard guidelines. • Tocilizumab[b] plus corticosteroids and supportive care, as described above.

[a] Use of filgrastim is not permitted 7 days prior until 10 days after TAC01-HER2 treatment (see Section 5.8)

[b] Maximum amount of tocilizumab per dose is 800 mg. If subject is unresponsive to 2-3 doses of tocilizumab, consider using siltuximab 11 mg/kg IV or anakinra 100 mg/day subcutaneous (SC) as per institutional cell therapy guidelines. Tocilizumab should be used as per label for CRS. In case of a tocilizumab-shortage, siltuximab or anakinra that are normally used as second line treatments as per institutional cell therapy guidelines can be used as first line.

[c] High-risk subjects include those with bulky disease, those with comorbidities, and those who develop early onset CRS within 3 days of TAC T cell infusion.

Neurotoxicity Management

Adapted from Neelapu 2018.

NT Grade	Management
Grade 1	• Vigilant supportive care; aspiration precautions; IV hydration. • Withhold oral intake of food, medicines, and fluids, and assess swallowing. • Convert all oral medications and/or nutrition to IV if swallowing is impaired. • Avoid medications that cause central nervous system depression. • Low doses of lorazepam (0.25–0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) can be used, with careful monitoring, for agitated subjects. • Neurology consultation. • Fundoscopic examination to assess for papilloedema as per Investigator discretion • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the subject has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible. • Daily 30 min EEG until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam 750 mg every 12 hours. • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Appendix E. • Consider anti-IL-6 therapy with tocilizumab[a] 8 mg/kg IV, if neurotoxicity is associated with concurrent CRS.
Grade 2	• Supportive care and neurological work-up as described for Grade 1 neurotoxicity. • Tocilizumab[a] 8 mg/kg IV if associated with concurrent CRS. • Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy or for neurotoxicity without concurrent CRS. • Consider transferring subject to ICU if neurotoxicity associated with Grade ≥2 CRS.
Grade 3	• Supportive care and neurological work-up as indicated for Grade 1 neurotoxicity. • ICU transfer is recommended. • Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 2 neurotoxicity and if not administered previously. • Corticosteroids as outlined for Grade 2 neurotoxicity if symptoms worsen despite anti-IL-6 therapy, or for neurotoxicity without concurrent CRS; continue corticosteroids until improvement to Grade 1 neurotoxicity and then taper. • Stage 1 or 2 papilloedema with CSF opening pressure <20 mmHg should be treated as per algorithm presented in Appendix E. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if subject has persistent Grade ≥3 neurotoxicity.

NT Grade	Management
Grade 4	• Supportive care and neurological work-up as outlined for Grade 1 neurotoxicity. • ICU monitoring; consider mechanical ventilation for airway protection. • Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 neurotoxicity. • High-dose corticosteroids continued until improvement to Grade 1 neurotoxicity and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. • For convulsive status epilepticus, treat as per algorithm in Appendix E. • Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral edema, should be treated as per algorithm in Appendix E.
[a] Maximum amount of tocilizumab per dose is 800 mg. If subject is unresponsive to 2-3 doses of tocilizumab, consider using siltuximab 11 mg/kg IV or anakinra 100 mg/day SC as per institutional cell therapy guidelines. Tocilizumab should be used as per label for CRS. In case of a tocilizumab-shortage, siltuximab or anakinra that are normally used as second line treatments as per institutional cell therapy guidelines can be used as first line.	

Status Epilepticus Management After TAC T cell Therapy

Adapted from Neelapu 2018.

Non-Convulsive Status Epilepticus

- Assess airway, breathing, and circulation, check blood glucose.
- Lorazepam* 0.5 mg IV, with additional 0.5 mg IV every 5 minutes, as needed, up to a total of 2 mg to control electrographic seizures.
- Levetiracetam 500 mg IV bolus, as well as maintenance doses.
- If seizures persist, transfer to ICU, and treat with phenobarbital loading dose of 60 mg IV.
- Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 hours for 3 doses; levetiracetam 1,000 mg IV every 12 hours; phenobarbital 30 mg IV every 12 hours.

Convulsive Status Epilepticus

- Assess airway, breathing, and circulation, check blood glucose.
- Transfer to ICU.
- Lorazepam* 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures.
- Levetiracetam 500 mg IV bolus, as well as maintenance doses.
- If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV.
- Maintenance doses after resolution of convulsive status epilepticus are lorazepam 0.5 mg IV every 8 hours for 3 doses; levetiracetam 1,000 mg IV every 12 hours; phenobarbital 1–3 mg/kg IV every 12 hours.
- Continuous electroencephalogram monitoring should be performed if seizures are refractory to treatment.

*Lorazepam is the recommended benzodiazepine because it is short-acting, compared with diazepam, and has been widely used in the management of seizures.

Raised Intracranial Pressure Management After TAC01-HER2 Therapy

Adapted from Neelapu 2018.

Stage 1 or 2 papilloedema* with CSF opening pressure of <20 mmHg without cerebral edema

- Acetazolamide 1,000 mg IV, followed by 250–1,000 mg IV every 12 hours (adjust dose based on renal function and acid–base balance, monitored 1–2 times daily)

Stage 3, 4, or 5 papilloedema* with any sign of cerebral edema on imaging studies or a CSF opening pressure of ≥20 mmHg

- Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for Grade 4 neurotoxicity.
- Elevate head end of the subject's bed to an angle of 30 degrees.
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg but maintained for no longer than 24 hours.
- Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below):
- Mannitol: Initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40.
- Hypertonic Saline: Initial 250 mL of 3% hypertonic saline; maintenance at 50-75 mL/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/L.
- For Subjects with Imminent Herniation: Initial 30 ml of 23.4% hypertonic saline; repeat after 15 minutes, if needed.
- If subject has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg.
- Consider neurosurgery consultation and IV anesthetics for burst-suppression pattern on electroencephalography.
- Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

*Papilloedema grading should be performed according to the modified Frisén scale.

Diagnostic Criteria for TAC T Cell Related MAS/HLH

Adapted from Neelapu 2018.

A subject might have MAS/HLH if he/she had a peak serum ferritin level of >10,000 ng/mL during the cytokine-release syndrome phase of TAC T cell therapy (typically the first 5 days after cell infusion for CAR T cell therapy) and subsequently developed any 2 of the following:

- Grade ≥3 increase in serum bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) levels*.
- Grade ≥3 oliguria or increase in serum creatinine levels*.
- Grade ≥3 pulmonary edema*.
- Presence of hemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry TAC; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage- activation syndrome.

*Grading as per Common Terminology Criteria for Adverse Events, version 5.0.

TAC T Cell Related MAS/HLH Management Recommendations

Adapted from Neelapu 2018.

MAS/HLH should initially be managed according to the guidelines for CRS (Appendix E), with appropriate subsequent laboratory testing to monitor response to treatment. If the results of these tests reveal no improvement within 48 hours, escalation of treatment should be considered.

- Manage Grade ≥3 organ toxicity with anti-IL-6 therapy + corticosteroids as per the CRS treatment algorithm (Appendix E).
- Monitor blood ferritin, lactate dehydrogenase, fibrinogen, transaminases, bilirubin, creatinine levels.

If no improvement is seen after 48 hours, consider

- Adding etoposide to treatment.
- Consider intrathecal cytarabine for neurotoxicity.

APPENDIX F. RESPONSE CRITERIA

Time Point Response: Subjects with Target (+/– Non-Target) Disease			
Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=non-evaluable			

Time Point Response: Subjects with Non-Target Disease Only		
Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not All Evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=non-evaluable		
a 'Non-CR/Non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.		

Best Overall Response When Confirmation of CR and PR Required		
Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=non-evaluable

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

APPENDIX G. ECOG SCALE (AND CONVERSION FROM KARNOFSKY SCALE)

Adapted from Oken 1982.

ECOG Status	ECOG Grade	Karnofsky Grade	Karnofsky Status
Fully active, able to carry on all pre-disease performance without restriction	0	100	Normal, no complaints
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	1	90	Able to carry on normal activities. Minor signs or symptoms of disease
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	1	80	Normal activity with effort
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	2	70	Care for self. Unable to carry on normal activity or to do active work
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	2	60	Requires occasional assistance, but able to care for most of his needs
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3	50	Requires considerable assistance and frequent medical care
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3	40	Disabled. Requires special care and assistance
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	4	30	Severely disabled. Hospitalization indicated though death not imminent
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	4	20	Very sick. Hospitalization necessary. Active supportive treatment necessary
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	4	10	Moribund
Dead	5	0	Dead

APPENDIX H. DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-RELATED AES ASSOCIATED WITH PEMBROLIZUMAB

General instructions:

1. Severe and life-threatening immune-related adverse events (irAEs) should be treated with intravenous (IV) corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood, or mucus in stool with or without fever) and of bowel perforation (ie. peritoneal signs and ileus) Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
				IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Neurological Toxicities	Grade 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		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a. AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal
b. AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal
c. AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
d. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.
e. Events that require discontinuation include but are not limited to encephalitis and other clinically important irAEs (e.g., vasculitis and sclerosing cholangitis).

APPENDIX I. PEMBROLIZUMAB INFUSION REACTION DOSE MODIFICATION AND TREATMENT GUIDELINES

NCI 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., 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 participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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 participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.