16.1.9 Statistical Analysis Plan

16.1.9.1 Statistical Analysis Plan for Protocol FF01 – Final Version 6.0 (31 Mar 2021) 2

STATISTICAL ANALYSIS PLAN
FOR PROTOCOL FF01

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Protocol Number:	FF01	
Protocol Name	VANCE	
Protocol Title:	A Multicenter, Randomized, Open-label, Phase III Clinical Trial of Gemcitabine and Carboplatin followed by Epstein-Barr Virus-specific Autologous Cytotoxic T-Lymphocytes versus Gemcitabine and Carboplatin as First Line Treatment for Advanced Nasopharyngeal Carcinoma Patients	
Phase	III	
Protocol Date / Version:	01 May 2020/ Version 12	

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Plan Version:	Final Version 6.0		
Plan Date:	31 March 2021		

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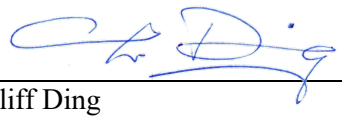
SAP Version:	Final Version 6.0
SAP Date:	31 March 2021

I have read and approve the Statistical Analysis Plan specified above and agree on its content:



30MAR2021

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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation/Acronym	**Definition**
AE	Adverse Event
ASA	American Statistical Association
AUC2	Carboplatin
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CI	Confidence Interval
CP	Conditional Power
CR	Complete Response
eCRF	Electronic Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocytes
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FU	Follow-up
GC	Gemcitabine and Carboplatin
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Safety Monitoring Committee
ITT	Intent to Treat
IV	Intravenous
KM	Kaplan Meier
LTFU	Lost to Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
MRI	Magnetic Resonance Imaging
NCCS	National Cancer Center Singapore
NCI	National Cancer Institute
NPC	Nasopharyngeal Carcinoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
QoL	Quality of Life

RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TEAEs	Treatment Emergent Adverse Events
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the clinical trial protocol FF01, sponsored by Tessa Therapeutics Ltd.. The reader of this SAP is encouraged to review the complete protocol, as this plan contains only a limited overview of protocol information and related data issues. The main objective of the plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this SAP are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this SAP will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents were reviewed in preparation of this SAP:

- Protocol Version 12, 01 May 2020
- Annotated eCRFs
- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)
- ASA Ethical Guidelines for Statistical Practice (1999) [1]
- The Royal Statistical Society: Code of Conduct (2014) [2]
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996) [4]
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998) [5]

2. PROTOCOL DESIGN

2.1 Design Overview

This study is a multi-center, randomized, open label, Phase III clinical trial.

Subjects with metastatic or locally recurrent EBV-positive NPC not amenable to further curative chemoradiation or surgery are eligible for this study. Eligible subjects are biopsy proven (whether earlier or at diagnosis of de novo advanced disease), non-keratinizing and/or undifferentiated carcinoma of the nasopharynx (EBV-related) who have not received first line chemotherapy for the treatment of advanced NPC.

Approximately 30 sites located in Asia and/or United States will enroll subjects in this

study. Three hundred and thirty (330) eligible subjects will be randomly allocated to receive treatment from either Arm A (GC and EBV-specific CTL) or Arm B (GC alone) in a 1:1 ratio using a stratified block randomization scheme. The stratification variables are country and disease stage (metastatic vs. locally recurrent).

2.2 Protocol Objective(s)

The primary objective is to assess the efficacy of EBV-specific CTL following first line chemotherapy compared to chemotherapy alone in terms of Overall Survival (OS) of subjects with advanced NPC.

The secondary objectives are:

- Evaluate milestone 2, 3 and 5-year Overall Survival rates for the two treatment arms
- Assess progression-free survival (PFS) for the two treatment arms
- Compare the Overall Response Rate (ORR), Clinical Benefit Rate (CBR) and Quality of Life (QoL) between the two treatment arms
- Assess safety of both treatment arms

The exploratory objectives are:

- Demonstrate persistence of EBV specific immune response in Arm A
- Evaluate biomarkers of response to therapy and in relation to outcome indices
- Develop a predictive biomarker classifier

2.3 Clinical Trial Duration

This trial is divided into three study phases, Pre-treatment, treatment and follow-up phases. These three phases are detailed here.

Pre-treatment Phase: All pre-treatment screening procedures to be completed within 4 weeks prior to initiating 1st chemotherapy.

Treatment Phase:

- Arm A: GC and EBV-specific CTL

1) Stage 1: Chemotherapy involving 4* cycles of gemcitabine (1000 mg/m^2) and carboplatin (AUC2), *with the option of an additional 1 to 2 cycles (i.e.: up to a total of 6 cycles) when the EBV-specific CTLs are not ready for infusion after the end of chemotherapy cycle 4 (EOC4) and patient's EOC4 evaluation scan shows CR, PR, SD

2) Stage 2: Immunotherapy involving 6 cycles of EBV-specific CTL infusion ($1x10^8$ cells/m^2)

After randomization, subjects in Arm A will have their peripheral blood taken for the establishment of cytotoxic T-cell line and EBV transformed LCL (CTL). Certain Arm A patients may have their blood taken for research evaluation purposes (refer section 6 for schedule of study procedures).

Within 4 weeks of obtaining informed consent, patients will commence combination gemcitabine and carboplatin chemotherapy for 4 cycles, with the option of an additional 1 to 2 cycles (i.e.: the 5th and 6th chemotherapy cycles up to a total of 6 cycles) if the EBV-specific CTLs are not ready for infusion after EOC4 and the patient's evaluation scan after the 4th cycle of chemotherapy shows CR, PR, SD , or if patients have not received the first infusion of EBV-specific CTLs, patients will remain in Stage 1 to continue receiving combination of gemcitabine and carboplatin chemotherapy for a total of 6 cycles and will not proceed to Stage 2. Patients who have already received their first EBV-specific CTL infusion will continue to receive the rest of their infusions as per treatment schedule.

Response evaluation using computed tomography (CT)/ magnetic resonance imagining (MRI) scan will be performed before the 3rd cycle of chemotherapy. The response to chemotherapy will be noted (i.e. CR, PR, SD or PD). Patients who are assessed as PD on imaging assessment may decide to seek alternative treatment based on the attending clinician's advice.

A second evaluation using CT/MRI scan will be repeated after the 4th cycle of chemotherapy, or before commencement of EBV-specific CTL infusions..

Refer to Figure 2-1 Study Schema for further details.

Subjects will be assessed for response to immunotherapy approximately 7 weeks after the first EBV-specific CTL infusion using CT/MRI scan. Evaluation CT/MRI scans will initially be repeated approximately 7 weeks after receipt of each EBV-specific CTL infusion. Following the end of treatment, patients will be followed up on survival status (Refer to Schedule of Assessment [Arm A] table). Subjects who demonstrate clinical benefit (CR, PR, and SD) to the first 2 cycles of immunotherapy will continue with immunotherapy for the remainder of the study. Subjects who are assessed as asymptomatic

PD on imaging assessment can continue with EBV-specific CTL based on the attending clinician's discretion. This is based on the known biological and clinical fact that optimal immunotherapy responses may be delayed and frequency-dependent.

Treatment for Arm A is expected to last approximately 13 months (Stage 1 – 4 to 6 months; Stage 2 – 6 to 7 months).

An End of Treatment assessment will be conducted approximately 30 days after the last CTL infusion.

- **Arm B**: GC only

Arm B consists of 6 cycles of IV gemcitabine (1000 mg/m^2) and IV carboplatin (AUC2). After randomization, subjects in arm B may have their peripheral blood taken for research purposes before commencement of chemotherapy.

Within 4 weeks of obtaining informed consent, subjects will commence combination gemcitabine and carboplatin chemotherapy for a total of 6 cycles. An evaluation CT/MRI scan will be performed after the second and then after the 4th and 6th cycle of chemotherapy. The response to chemotherapy will be noted (i.e. CR, PR, SD or PD). Subjects who are assessed as PD on imaging assessment may decide to seek alternative treatment based on the attending clinician's advice.

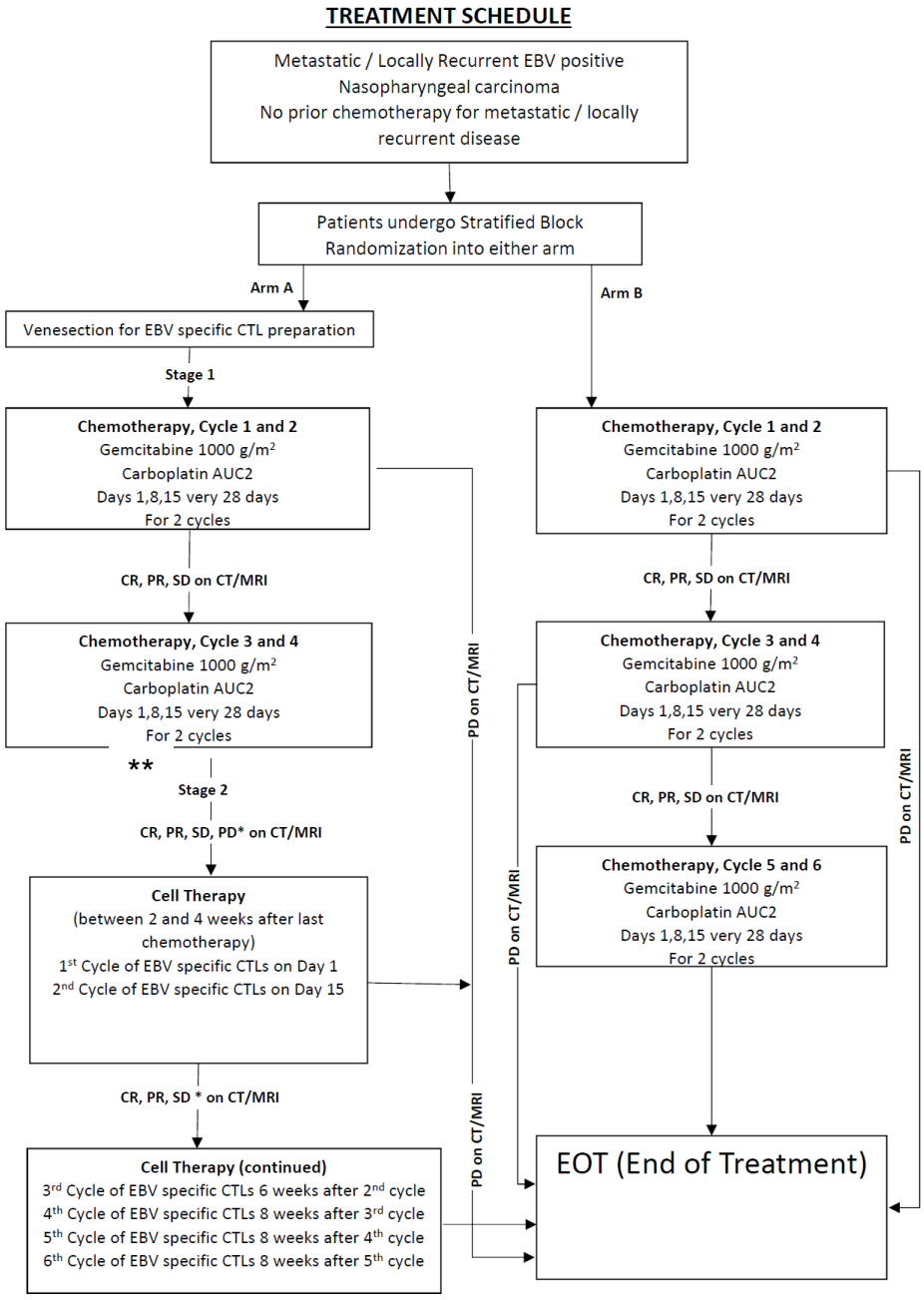
Treatment for Arm B is expected to last approximately 6 months.

An End of Treatment assessment will be conducted approximately 30 days after the last dose of chemotherapy.

Follow-up Phase: Following EOT, survival status will be followed up every 12 weeks (+/- 5 days).

The duration of participation is up to 4 weeks of screening until death (or lost to follow up). The study schema is presented in Figure 2-1.

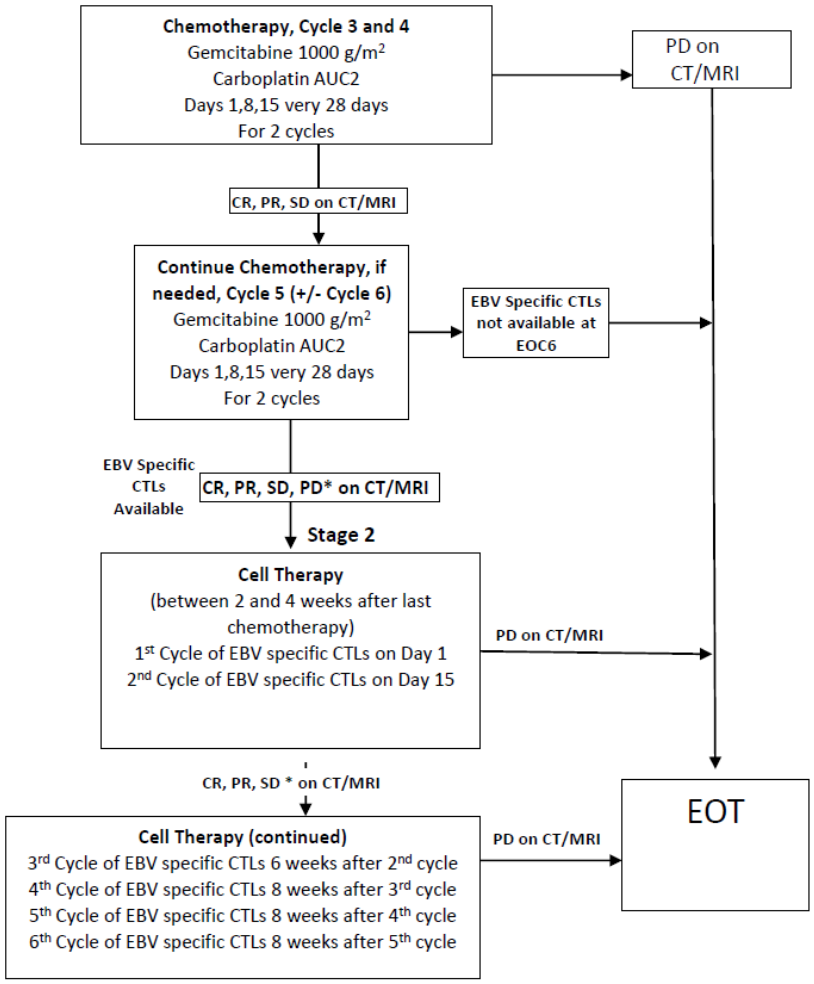
Figure 2-1 Study Schema



* Off Study treatment if: PD during or after CTL infusion, or during chemotherapy and symptomatic. Based on clinician discretion, if asymptomatic PD, may receive CTL treatment. If CTLs not available after EOC4, refer below.

** If patients have not received the first infusion of EBV-specific CTLs, patients will remain in Stage 1 to continue receiving combination of gemcitabine and carboplatin chemotherapy for a total of 6 cycles and will not proceed to Stage 2.

**** If EBV-specific CTLs are not available after EOC4**



* Off Study treatment if: PD during or after CTL infusion, or during chemotherapy and symptomatic. Based on clinician discretion, if asymptomatic PD, may receive CTL treatment. If CTLs not available after EOC6, patient will proceed to EOT.

** If patients have not received the first infusion of EBV-specific CTLs, patients will remain in Stage 1 to continue receiving combination of gemcitabine and carboplatin chemotherapy for a total of 6 cycles and will not proceed to Stage 2.

2.4 Study Treatments

2.4.1 Treatment Groups

This is a comparator study: Arm A (GC and EBV-specific CTL) versus Arm B (GC alone) as detailed in Section 2.3.

2.4.2 Randomization, Blinding, and Stratification

This study will be conducted at approximately 30 sites in Asia and/or United States. 330 subjects are planned to be enrolled. All eligible subjects will be centrally randomized to receive either Arm A (GC and EBV-specific CTLs) or Arm B (GC alone) in a 1:1 ratio using a stratified block randomization scheme. The stratification variables are country (Malaysia, Singapore, US, Thailand, Taiwan) and disease stage (metastatic versus locally recurrent). Within each stratum, subjects will be allocated with equal probability to either treatment in Arm A or treatment in Arm B and the randomization system will be set up in such a way that there is a 1:1 balance between the treatment groups from the different strata.

Since this is an open label study, on-site study personnel will have knowledge of the treatment assignments after randomization and throughout the study. To avoid any susceptible selection bias, a stratified block randomization scheme with a mixed block size will be used and the blocks will be blinded until trial closure to all research personnel except the block generating statistician.

2.5 Study Assessments

2.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is overall survival (OS).

2.5.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

- Milestone 2, 3 and 5-year Overall Survival rates
- Progression-free survival (PFS)
- Overall response rate (ORR)
- Clinical benefit rate (CBR)
- Quality of life (QoL)

2.5.3 Safety Assessments

Safety will be assessed based on the following assessments:

- Incidence and severity of treatment-emergent adverse events (TEAEs), including serious adverse events and adverse events resulting in permanent discontinuation of protocol-defined therapy.
- Changes in selected laboratory test results (i.e.,
    - Serum chemistry including urea, serum creatinine, sodium, potassium, chloride, bicarbonate, glucose, bilirubin, albumin, ALT, AST, ALP, total protein; and
    - Full blood count (FBC) including hemoglobin, hematocrit, RBC count, Platelets count, total leukocyte count, neutophils, eosinophils, basophils, monocytes, absolute neutophil count)
- Changes in vital signs including systolic and diastolic blood pressure and pulse
- Changes in electrocardiogram (ECG) results
- Changes in physical examination results
- Pregnancy for subjects who are women of child bearing potential (WOCBP) and partner/spouse pregnancies of male subjects (if consent is obtained).

3. SAMPLE SIZE DETERMINATION, STATISTICAL POWER, AND SIGNIFICANCE LEVEL

A total of 330 subjects will be enrolled and randomized in a 1:1 ratio to Arm A and Arm B. The final analysis will be performed when 280 deaths have been observed. This sample size is sufficient to detect a 33% reduction in the risk of death in Arm A, as compared with Arm B (hazard ratio, 0.67) using a 2-sided log-rank test with 71% power and an overall significance level of 5%. Given that subjects receiving first line conventional chemotherapy at the NCCS have an estimated median OS of 18 months and assuming survival times are exponentially distributed, this sample size and target number of events also allows a corresponding detection of about 9 months difference in median OS between the 2 arms. A hazard ratio of 0.67 or better is considered to still be clinically meaningful taking into consideration other treatment options in metastatic incurable solid tumors, where an additional minimum of 3 months' benefit (equivalent to a hazard ratio of 0.85 or better) in median overall survival is considered meaningful. An accrual period of about 5.5 years, an additional 3 years of follow-up, a dropout rate of 10% and a 6-month delay in separation of the survival curves are factored in the sample size calculations. Sample size

was calculated using nQuery Advanced 8.3.

The final analysis may be triggered when 280 deaths have occurred to conclude the OS result, or at the discretion of the Sponsor if it is not likely to reach 280 OS events in a reasonable timeframe, to summarize the OS findings which may not be conclusive. No interim analysis is planned for this study.

4. HYPOTHESIS TO BE TESTED

The clinical trial is designed to primarily test if Overall Survival among subjects with advanced NPC who receive EBV-specific CTL (Arm A) following first line chemotherapy differs compared to first line chemotherapy (Arm B).

Statistical Hypothesis:

Hazard ratio – the relative risk of death based on comparison of the rates in each group. The hazard ratio is calculated using a ratio of Arm A hazard rate by Arm B hazard rate.

Hypothesis to be tested:

H_0: HR=1
H_1: HR≠1

5. ANALYSIS POPULATIONS

The analysis and reporting of the data from this study will be performed using the following analysis populations:

5.1 Intent to Treat (ITT) Population

The intent-to-treat (ITT) analysis population will be used for the primary analysis of efficacy in this study, and is defined as all randomized subjects. Subjects will be included in the treatment group corresponding to the group that they were randomized to (i.e., if a subject is randomized to Arm B and gets treated with immunotherapy, the subject will be included in Arm B for the ITT analysis).

5.2 Safety Population (as treated)

The safety population will include all randomized subjects who receive at least one dose of chemotherapy treatment. Subjects will be analyzed in the treatment arm corresponding to the actual treatment received.

6. DATA CONVENTION AND RELATED DEFINITIONS

6.1 Baseline Definition

For purposes of all analyses presented here, the baseline value is defined as the last available value obtained prior to administration of any study drug.

6.2 Multiple assessments within a visit window

For multiple scheduled or unscheduled assessments that fall within a protocol-specified visit, the last measured value will be used for the analysis.

All collected data will be listed.

6.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified.

6.3.1 Handling of Missing Data for Overall Survival

Patients known to be deceased without a date of death will be assigned an OS event date which is the mid-point between the last date known to be alive and the date the patient's death becomes known.

6.4 Definitions of Efficacy and Other Endpoints

6.4.1 Age

Age will be calculated as:

Age (years) =
= year of randomization - year of birth, if months and day of randomization < month and day of birth, or
= year of randomization - year of birth +1, otherwise

6.4.2 Overall Survival (OS)

OS is defined as the duration in months from the day of randomization until death from any cause for a patient known to be deceased, or censored at the last contact date for a patient known to be alive or lost to follow-up. The last contact date is the last date a patient was known to be alive as documented in the database.

OS = (Death Date/Last Contact Date - Randomization Date + 1) / 30.4

6.4.3 Progression-free Survival (PFS)

PFS is defined as the duration from randomization to the first occurrence of documented disease progression (based on imaging results) or death from any cause, whichever occurs first. Subjects free from disease progression who are alive or lost to follow-up are censored at the date of last tumor assessment, as per the December 2018 FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics', Subjects who commence new anticancer treatment will be censored using the date of last adequate radiological assessment prior to initiation of new anticancer treatment.

PFS = (Disease Progression Date or Death Date – Randomization Date + 1) / 30.4

Note: One month is considered 30.4 days.

6.4.4 Overall Response Rate (ORR)

Response will be assessed using CT/ MRI based on RECIST version 1.1. The ORR for each treatment arm will comprise of the proportion of patients who achieve a Best Overall Response (BOR) of CR or PR while on treatment (until End of Treatment visit), taking as reference the tumour measurement at baseline. The ORR for Arm A will thus assess the best response achieved during combined chemo-immunotherapy.

6.4.5 Clinical Benefit Rate (CBR)

The CBR is defined as the proportion of patients who achieve CR, PR or SD while on treatment (until End of Treatment visit), taking as reference the tumour measurement at baseline. The CBR for Arm A will thus assess the best clinical benefit achieved during combined chemo-immunotherapy.

Where SD is believed to be the best response, it must be reflected in 2 consecutive assessments.

6.4.6 Quality of Life (QoL)

QoL will be assessed by using EORTC QLQ-C30 questionnaire. The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. A transformation to a scale of 0 – 100 would be carried out prior to analysis for all raw scores, with a higher score representing a higher level of functioning or higher level of symptoms. Items will be scaled and scored using the recommended EORTC procedures [7]. Descriptive statistics relating to completion of the items at each time point and the reason for non-completion will be tabulated.

7. SUMMARIZING AND TABULATING THE COLLECTED DATA

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum, maximum, 25th and 75th percentile) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

All the efficacy analyses presented here will be conducted using the ITT and Safety populations. All safety analyses will be conducted using the Safety population.

7.1 Disposition, Demographic and Baseline Characteristics Data

7.1.1 Subject Disposition and Study Treatment Completion Status

The following will be summarized in the disposition table:

- The number of subjects who signed informed consent
- The number of subjects who signed informed consent but were not randomized
- The number of subjects who were randomized by treatment group
- The number of randomized subjects who received any study treatment by treatment group
- The number of randomized subjects who received CTL (arm A only)
- The number of subjects who completed the study treatment by treatment group

- The number of subjects who discontinued prior to completion of study treatment by treatment group
- The number of subjects lost to follow-up or withdrew consent

Reasons for discontinuation prior to completion will also be summarized descriptively by treatment group.

In addition, there will also be a listing of all discontinued subjects, which will provide the clinical trial center, treatment group, and the specific reason for discontinuation.

7.1.2 Analysis Populations

The number of subjects in the ITT (i.e., all randomized subjects) and Safety populations will be tabulated and the reason for any subject exclusion from one or more analysis populations will be summarized.

7.1.3 Protocol Deviations

This study is intended to be conducted as specified in the protocol. In the event of significant deviation from the protocol the investigator (or a designee) will contact the sponsor and a decision will be made regarding the subject's continuation in the study. The deviations occurring during the clinical trial will be collected and presented as by subject listing and will also be summarized descriptively.

Major protocol deviations will also be identified by the sponsor prior to final database lock and this will be used to identify the Per Protocol analysis population for supportive efficacy analysis. Per ICH major protocol deviations include:

- Informed consent deviation
- Entrance criteria deviation
- Withdrawal criteria deviation
- Received wrong treatment or incorrect dose
- Received an excluded medication

7.1.4 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age, gender, ethnicity
- Height, weight, BSA

- Time since diagnosis of most recent relapse/ progression
- Disease stage
- Eastern Cooperative Oncology Group (ECOG) performance status
- Histological findings
- Country

Demographic and baseline characteristics will be summarized for ITT and Safety populations. Age (years) will be summarized as a continuous variable and categorical variable (<65 years vs. ≥65 years). By subject listing of all demographic and baseline characteristics will also be provided.

7.1.5 Medical History

Medical history data will be coded using MedDRA dictionary and summary will be presented using SOC and PT. All medical history will also be listed presented as a by-subject listing.

7.1.6 Venesection and HLA-Typing

All the data from venesection (blood sampling) for EBV specific CTL preparation and HLA-typing will be presented as a by-subject listing. This will only be for subjects randomized to Arm A.

7.1.7 HBsAg/HIV Antibody

All the data from HBsAg/ HIV antibody or other confirmatory test will be presented as a by-subject listing.

7.1.8 Prior and Concomitant Medications

Previous and concomitant medications will be coded using the World Health Organization (WHO) dictionary. Concomitant medications will be summarized by frequency of drug classification. Previous and concomitant medications will be presented in a data listing.

7.1.9 Concomitant Therapy

Concomitant therapy data will be coded using the World Health Organization (WHO) dictionary. Concomitant medications will be summarized by frequency of WHO drug classification. Concomitant therapy data will also be presented in a data listing.

7.1.10 Post-study Antineoplastic Therapy

Antineoplastic therapy data will be categorized as follows:

- Immune-checkpoint inhibitors
- Chemotherapy regimens
- Other anticancer regimens
- Surgery
- Radiation

Antineoplastic therapy data will be summarized by frequency of WHO drug classification. Antineoplastic therapy data will also be presented in a data listing.

7.1.11 Treatment Exposure and Compliance

The total number of treatment cycles initiated and completed for each subject will be tabulated. The summary for Arm A will include exposure of chemotherapy (i.e., gemcitabine and carboplatin) & immunotherapy, and that for Arm B will include exposure of chemotherapy (i.e., gemcitabine and carboplatin). Relative dose intensity (RDI) will also be computed and these data will be further summarized by calculating the mean, standard deviation, median, 25th and 75th percentile, minimum and maximum values for each treatment arm.

Exposure to a treatment is defined as:

Exposure = (date of last dose – date of first dose +1) / 30.4, in the unit of month.

The RDI of gemcitabine or carboplatin is defined as:

$$RDI = 100\% \times \frac{Total\ dose\ received \times planned\ treatment\ duration}{Total\ dose\ planned \times actual\ treatment\ duration},$$

where

- Total dose received = cumulative dose received in the prescribed unit (mg/m^2 for gemcitabine, AUC for carboplatin, and $\times 10^8$ cells/m^2 for EBV-specific CTLs);
- Total dose planned = number of doses planned × the prescribed dose (1000 mg/m^2 for gemcitabine, AUC2 for carboplatin, and 1×10^8 for EBV-CTLs);

- Actual treatment duration = date of last dose – date of first dose +6 or 13 (6 if the last dose received is the Day 1 or Day 8 dose of a cycle, 13 if it is the Day 15 Dose);
- Planned treatment duration = the length of time in days it would take for the number of doses a patient actually received per study treatment plan, including the planned resting period for the last dose.

The number and proportion of subjects with one or more dosage modification (i.e., reduction or delay) of study drug will be tabulated and the primary reason for dosage modification.

7.2 Analysis of Efficacy Data

All secondary efficacy analyses will be performed for the ITT and Safety populations.

7.2.1 Analysis of the Primary Endpoint

The primary endpoint for this study is OS, as determined by the definition in Section 0.

Median OS, as well as survival rates at 2, 3, and 5-years, along with the corresponding 95% CIs, will be estimated using Kaplan-Meier product-limit method. HR and the 95% CI will be estimated using Cox proportional hazards regression, stratified by country and disease stage. Between-treatment comparison will be assessed using stratified log-rank test. The unstratified estimates and comparison will also be performed.

The Score likelihood test (i.e., which is equivalent to log-rank test) from the Cox proportional hazards model will be used to assess the difference between treatment arms.

In addition, the Kaplan-Meier plot will be generated, and the Kaplan-Meier method will also be used to estimate the median, 25th and 75th percentiles, minimum and maximum and the 95% confidence interval for the median time (months) to death from any cause for the treatment groups. These summaries will be presented for the ITT and Safety populations.

7.2.2 Analysis of Secondary Endpoints

7.2.2.1 Progression-Free Survival (PFS)

PFS will be summarized using methods similar to the methods used for OS. The primary analysis of PFS will be right-censored, based on the FDA guidance 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Dec 2018'.

7.2.2.2 Overall Response Rate (ORR)

The definition of ORR is presented in Section 0. The ORR estimate and the associated 95% CI for each arm will be presented. The difference in ORR between treatment groups and the 95% CI for the difference will be estimated using logistic regression with the stratification factors (i.e., country and disease stage) included in the model. In addition, the odds ratio and its 95% CI from the logistic regression will also be presented.

7.2.2.3 Clinical Benefit Rate (CBR)

The definition of CBR is presented in Section 6.10.6. The CBR estimate and the associated 95% CI for each arm will be presented. The difference in CBR between treatment groups and the 95% CI for the difference will be estimated using logistic regression with the stratification factors included in the model. The odds ratio and its 95% CI will also be presented.

7.3 Analysis of Safety Data

The Safety Population will be used for all analyses of safety. All safety parameters will be presented descriptively and as data listings. Safety and tolerability will be assessed by the incidence of treatment emergent adverse events (TEAEs) (see below), change from baseline in selected laboratory parameters, vital signs parameters and ECGs. Additionally, for Arm A, safety will also be summarized separately for the periods before and after receipt of the first CTL infusion. Only events occurring prior to 8 weeks (56 calendar days) after receipt of the last dose of study treatment will be included in the analysis.

7.3.1 Adverse Events

Adverse event terms recorded on the eCRF will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) version xxx. The severity of AEs will be graded according to the CTCAE v4.03, as assessed by investigators.

Treatment-emergent AEs (TEAEs) are defined as those with onset date between the date of the first dose of study treatment and 8 weeks (56 calendar days) after the last dose of study treatment, inclusive.

Incidence of TEAEs will be tabulated by treatment arms according to the actual study treatment received, and the worst toxicity grade during the treatment period. Frequency distribution of TEAEs in terms of MedDRA system organ class (SOC) and preferred term (PT) will be based on the number of patients who reported the AE at least once and the worst toxicity grade if there were multiple occurrences of the same AE in various grades.

The following AE summaries will be generated:

- ALL TEAEs by the worst toxicity grade
- TEAEs of toxicity grade 3 or higher
- Serious AEs
- TEAEs by relatedness to study treatment (Attributions of definite, probable, and possible will be classified as related; unlikely and unrelated will be classified as not related).
- Related TEAEs of toxicity grade 3 or higher
- Related serious AEs
- TEAEs resulting in discontinuation of protocol therapy
- TEAEs with outcome of death

All AEs, including TEAEs, will be included in individual subject listings. All SAEs with details of each event will also be listed.

7.3.2 Clinical Laboratory Assessments

The changes in laboratory values will be summarized descriptively for each scheduled protocol assessment time point. Change from baseline will be calculated for all post-baseline assessments. All safety laboratory tests will be graded using CTCAE version 4.03, as appliable.

- Serum chemistry including urea, serum creatinine, sodium, potassium, chloride, bicarbonate, glucose, bilirubin, albumin, ALT, AST, ALP, total protein; and
- Full blood count (FBC) including hemoglobin, hematocrit, RBC count, Platelets count, total leukocyte count, neutrophils, eosinophils, basophils, monocytes, absolute neutrophil count)

All hematology and chemistry lab tests gradable by CTCAE v4.03 will be summarized by toxicity grade using a shift table at each protocol defined post-baseline visit as well as the worst toxicity grade during the study against baseline.

All hematology and chemistry lab tests will be summarized by below or within or above normal limits using a shift table at each protocol defined post-base line visit against baseline.

For change from baseline summaries, subjects with an undefined change from baseline because of missing data at a given time point, will be excluded from summaries at that time point. All available laboratory data will be included in individual subject listings. Laboratory results will be reported in subject listings according to conventional units.

7.3.3 Vital Signs

Vital sign results (systolic and diastolic blood pressure and pulse rate) will be summarized descriptively for each scheduled protocol time point. Changes will be calculated relative to the assessments at baseline and on the first day of each cycle. For change from baseline summaries, subjects with an undefined change from baseline because of missing data at a given time point, will be excluded from summaries at that time point.

7.3.4 Electrocardiogram (ECG)

ECG results will be listed and summarized in terms of the number and percentage of subjects with abnormal and clinically significant, abnormal and not clinically significant, and normal findings at the scheduled and unscheduled protocol assessment time point. Additionally, descriptive statistics will be tabulated for changes from normal during baseline evaluation to abnormal and clinically significant findings during any assessment time point. Subjects with missing data for a given time point will not contribute to the

tabulations for that time point.

7.3.5 Research Blood

Research bloods (approximately up to 40 mL, as much as possible), will be collected before commencement of cycle 1 chemotherapy and after completion of every 2 cycles of chemotherapy. The timing of blood collections for each subject will be reported as a by-subject listing.

7.3.6 Urine Pregnancy Test

All data from Urine Pregnancy test will be presented as a by-subject listing.

7.4 Multicenter Clinical Trials

This is a multicenter clinical trial. However, site will not be considered as a stratification variable during the analysis. All data collected will be presented as a by-subject listing.

7.5 Multiple Testing and Comparisons

For the primary endpoint only one hypothesis will be tested.

For the secondary endpoints, the closed test procedure will be used to protect the trial-wise error rate. The order of the endpoints is specified in Section **Error! Reference source not found.**; namely: Progression-Free Survival (PFS), Overall Response Rate (ORR), Clinical Benefit Rate (CBR) and Quality-of-Life (QoL).

7.6 Exploratory Analysis

7.6.1 Covariates

The efficacy analysis of the primary endpoint; namely: Overall Survival will be carried out with a single covariate of treatment arm. Covariate-adjusted analyses for the primary endpoint will be carried out as a supportive analysis using potential prognostic factors listed below. Only covariates that are found to be independently associated with OS (individual covariate p-value ≤ 0.05 will be retained in the final stratified Cox regression model.

- Age (<65 years vs. ≥65 years)
- Gender (Male vs. Female)

7.6.2 Subgroups

During preparation of the final analysis, exploratory subgroup analyses based on the following subgroups will be performed for the primary and secondary endpoints if the numbers allow.

- Age (<65 years vs. ≥65 years)
- Sex (Male vs. Female)
- Country
- Treatment center
- Disease stage (Metastatic vs. Locally recurrent)
- Applicable only for Arm A:
    - Number of cycles of GC chemotherapy received (≤4 vs. >4)

7.6.3 Other Exploratory Analyses

Exploratory analyses will be used to investigate the correlation between immune biomarker signatures and clinical outcomes (OS, PFS, ORR, CBR), and whether such correlations are dependent on the treatment received. In this way, both prognostic and predictive biomarkers will be explored. This will involve analyzing values at baseline to identify at the outset patients who are more likely to respond to therapy, but also post-baseline to understand how the changing biomarker profile through time correlates with clinical outcomes and response to therapy.

A multi-factorial approach, which encompasses measurements of multiple analytes, will be applied to take account of the balance and interaction between the immunostimulatory and immunosuppressive arms of both the cancer and the immune system. These exploratory analyses may include, but are not limited to, the following biomarkers of interest:

- EBV viral load
- Inhibitory leukocytes, including regulatory T-cells, monocytic and granulocytic MDSCs
- Anti-cancer cells such as effector memory CD8 T-cells

- Distinct classes of serum associated cytokines, including immune stimulatory markers such as IFNγ, and immune suppressive cytokines such IL10, and CCL22
- Transcriptome analysis from PBMCs to incorporate and validate proteomic measurements

Cox proportional hazards models will be used to explore associations between biomarkers and time-to-event endpoints such as OS and PFS, with treatment-by-biomarker interaction terms included in the model to test for predictive biomarkers. Generalized Linear Models will similarly be used to explore biomarker associations with binary endpoints (ORR, CBR, 2, 3 and 5-year OS). Due to the large number of hypotheses being tested, these analyses will be regarded as exploratory rather than confirmatory.

7.7 Sensitivity Analysis

7.7.1 Analyses to assess the impact of differential withdrawal of study treatment between arms

The current study schema allows subjects in study Arm B who experience progressive disease (PD) after 2 or 4 cycles of chemotherapy to go off study treatment, unless the progressive disease is asymptomatic at the discretion of the clinician. Subjects in Arm A who have progressive disease after 2 cycles of chemotherapy are allowed to go off study treatment, but those who experience disease progression after 4 cycles of chemotherapy are offered cell therapy rather than go off-study. The impact of this differential withdrawal of study treatment on the ITT analysis of the primary endpoint will be explored using the following sensitivity analyses.

7.7.1.1 Prognostic factors at baseline of subjects who progressed after 4 cycles of chemotherapy

Prognostic factors at baseline will be summarized descriptively for subjects who progressed after 4 cycles of chemotherapy versus those who did not, by treatment arm. This will include the same baseline covariates used as those that were significant in the multivariable model described in Section 6.8.

7.7.1.2 Censoring of subjects with progressive disease after 4 cycles of chemotherapy

A sensitivity Cox regression analysis will be performed of the primary endpoint wherein subjects from either treatment arm who exit the study due to progressive disease after 4 cycles of chemotherapy will be censored at the time of progression for analysis of the

primary endpoint of OS.

7.7.2 Association between the number of CTL infusions received and Overall Survival

It is of interest to investigate whether the efficacy of CTL therapy in Arm A subjects is dependent on the number of infusions received. There are inherent challenges to implementing this type of analysis, owing to what is referred to as 'immortal-time bias' (also known as 'survivor bias' or 'guarantee-time bias'). This bias occurs when a time-to-event endpoint is compared across groups defined by a classifying event occurring during follow-up. Hence, comparing survival by the number of CTL infusions received can be problematic, because a subject can only receive a certain number of infusions if they survive until that point.

It is hypothesized that a minimum of two CTL infusions is needed to demonstrate efficacy. The following three sensitivity analyses will be conducted in Arm A subjects to compare OS according to the number of CTL infusions received (<2 Vs ≥2), using Cox regression models stratified by country and disease stage (following the approach outlined by Giobbie-Hurder et. al. [10]):

- *Naïve estimator*
  A single binary covariate for the number of CTL infusions received (<2 Vs ≥2) will be included in the Cox regression model.
- *Conditional landmark analysis*
  Cox regression will be used with a single binary covariate for the number of CTL infusions (<2 Vs ≥2). The reference time or 'time zero' will equal the scheduled time point at which the 2nd CTL infusion should have been administered per protocol. Conditioning on this 'landmark' restricts the analysis to subjects who have survived up until this point, and answers the question 'among those subjects who are still alive at the scheduled time of the 2nd CTL infusion, what is the association between number of infusions (<2 Vs ≥2) and survival?'
- *Extended Cox model with time-varying covariate*
  A time-varying binary covariate indicating number of infusions received (<2 Vs

≥2) will be included in the Cox regression model.

The HR's (≥ 2 Vs < 2 CTL infusions), 95% CI's, and KM curves corresponding to each of the above analyses will be reported to assess whether treatment efficacy is dependent on the number of infusions received, and the extent to which the naïve estimator is confounded by immortal-time bias.

8. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The independent data monitoring committee (IDMC) will receive descriptive summary tables to aid in review of safety during their annual reviews. These tables will include demographics, treatment exposure, adverse events, serious adverse events, laboratory findings, physical examinations, vital signs and ECG.

9. APPENDIX 1 SCHEDULE OF ASSESSMENT (ARM A)

	Pre-Treatment	**Chemotherapy**			
	Screening (Baseline)	**Cycle 1 to 4[s] (Stage 1)**			**End of Cycle 2 & 4**
	-28 days	Day 1	Day 8	Day 15	
Time- Window	4 weeks from signing informed consent form to 1st chemotherapy dose	1. For Cycle 1 Day 1- within 4 weeks of obtaining informed consent 2. Subsequent cycles Day 1 - ±3 days 3. All cycles Day 8 and 15 - ±3 days 4. Total duration of each cycle should within 25 to 31 days from that cycle Day 1 dosing, unless due to treatment delay as per allowed by protocol			After Day 15, before dosing of next cycle
Informed Consent	X [##]				
Randomization	X [g]				
Blood Sampling for Immune Cell Preparation (Venesection; only if randomized into Arm A) [b]	X				
HLA-Typing (only if randomized into Arm A)	X				
Pre-Medication		X [d]	X [d]	X [d]	
Chemotherapy (Gemcitabine + Carboplatin)		X [e]	X [f]	X [f]	
Demographics	X				
Medical History and Medication History	X				
Physical Examination [++]	X	X [c]			
Vital signs (BP, PR)	X	X [c]			
Height	X				
Weight	X	X [c]			
ECOG Performance Status	X	X [c]			
Urine Pregnancy Test	X				
FBC [+]	X [n]	X [k]	X [k]	X [k]	
Serum chemistry [i]	X [n]	X [k]			
HBsAg / HIV Antibody or Other Confirmatory Test [a]	X				
ECG	X				
Research blood (At least 50 Arm A patients from sites in Singapore, Malaysia, Taipei and Taoyuan only)		X [d]			X [m]
Concomitant Medication / Therapy	X	X	X	X	X
AE/SAE evaluation [q]	X	X	X	X	X
CT or MRI scan for Tumor Response [j]	X [h]				X
QoL		X [d]			X
Survival Status		X	X	X	X

	Immunotherapy						End of Treatment (EOT)	Follow-up ^
	(Stage 2)							
	1st Infusion	2nd Infusion	3rd Infusion	4th Infusion	5th Infusion	6th Infusion		
Time- Window	≥14 days, ≤28 days from last dose of chemotherapy	14 days (±5 days) after 1st infusion of CTL	6 weeks (±5 days) after 2nd infusion of CTL	1. 8 weeks (±5days) after the previous infusion 2. Schedule may only be adjusted after discussion and approval by coordinating investigator and sponsor			EOT to be done at 30 days (± 5 days) after last dose ***	Survival status will be followed up every 12 weeks (± 5 days)
Pre-Medication	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]		
Immune Cell Infusion	X	X	X	X	X	X		
Physical Examination [++]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X	
Vital signs (BP, PR)	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X	
Weight	X	X	X	X	X	X	X	
ECOG Performance Status	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X	
FBC [+]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X	
Serum chemistry [i]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X	
ECG (as indicated)	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X	
Research blood (At least 50 Arm A patients from sites in Singapore, Malaysia, Taipei and Taoyuan only)	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]		
Concomitant Medication / Therapy	X	X	X	X	X	X	X	
AE/SAE evaluation [q]	X	X	X	X	X	X	X	
CT or MRI scan for Tumor Response [j]		X *	X **	X **	X **	X **	X	
QoL		X [o]		X [o]			X	
Survival Status	X	X	X	X	X	X	X	X

* To be done approximately 7 weeks (±5days) after 1st cycle of induction immunotherapy

** To be done approximately 7 weeks (±5days) after each cycle of maintenance immunotherapy

*** EOT to be done at 30 days (±5days), after last dose of therapy

**** If patients have not received the first infusion of EBV-specific CTLs, patients will continue receiving combination of gemcitabine and carboplatin chemotherapy for a total of 6 cycles and will not proceed to receive EBV-specific CTL infusion

^ Patients who completed treatment will be followed up on the assessments listed for Follow-up. Patients who commence salvage therapy will exit the study treatment. These patients will be followed up on survival status and initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment.

Written informed consent to be obtained after study has been fully explained to each subject prior to the conduct of any screening procedures or assessments

\+ FBC: Hemoglobin, Hematocrit, RBC count, Platelets, Total Leukocyte Count, Neutrophils, Eosinophils, Basophils, Monocytes, Absolute

Neutrophil count.

++ Includes, but not limited to the following systems: Head, Eye, Ear, Nose and Throat / Lymph Nodes / Cardiovascular / Thorax / Abdomen / Extremities / Skin and Mucosae / Musculoskeletal / Neurological

a Status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 4 weeks of screening

b Additional blood (approximately 200mL, up to 250 ml) may need to be taken if production of CTLs may fail or yield may be insufficient. If cell yield is still not sufficient (and it is confirmed that the low yield is not due to production process within control) after this additional blood is collected, subject will be withdrawn from the study treatment, undergo EOT visit and followed up on survival status and initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment. There should be at least a 14 days interval from the last dose of chemotherapy to the additional blood collection date. Additional blood collection should also be done at least 8 weeks after the initial venesection date. Lastly, Hb count (results must be within 7 days from date of additional blood venesection) must be ≥10 g/dL prior to blood collection.

c To be conducted before the start of each treatment cycle

d To be conducted before 1st dose of chemotherapy

e Patients with ANC <1000/mm^3 or Platelet count <100,000/mm^3 or Grade 3 and above AEs, on the first day of a new cycle will delay chemotherapy until recovery. They will have their FBC repeated at weekly intervals until recovery. Patients who experience delays of more than 28 days because of low neutrophil or platelet counts or Grade 3 and above AEs, will be taken off the study treatment. They will undergo EOT visit and followed up on survival status initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment

f Patients with ANC <1000/mm^3 or platelet <100,000/mm^3 or Grade 3 and above AEs, during Day 8 or Day 15 chemotherapy will have chemotherapy on that day delayed for up to a week. Should the condition persist past a week, chemotherapy will then be omitted and not replaced.

g To be conducted after eligibility confirmation, before venesection

h To be conducted only if last CT or MRI scan is not done within 4 weeks of C1D1

i Tests include Urea, Serum creatinine, Sodium, Potassium, Chloride, Bicarbonate, Glucose, Bilirubin, Albumin, ALT, AST, ALP, Total protein. Calcium and Magnesium to be performed only at Screening Visit.

j The method of assessment and the same technique (e.g. CT or MRI) should be used to characterize each identified and reported lesion shall be determined at baseline and remained throughout the study period.

k To be conducted before starting treatment.
Note: FBC, differential counts and Serum Chemistry within 3 days before the start of each chemotherapy cycle. FBC and differential counts within 3 days before dosing of Day 8 and Day 15 of each chemotherapy. FBC, differential counts, Serum Chemistry and research blood within 3 days before the start of each immunotherapy cycle. ECG will be performed before each cycle of immunotherapy

m To be conducted after completion of every 2 cycles of chemotherapy (end of cycle 2 & 4). End of cycle 4 must be a separate timepoint from 1st cycle of immunotherapy.

n FBC and differential counts, Serum Chemistry (results must be within 7 days from date of venesection of peripheral blood for preparation of EBV-LCL and subsequent cytotoxic T lymphocytes (CTL) generation)

o To be conducted after 2nd cycle of immunotherapy and before 3rd cycle of immunotherapy, and after 4th cycle of immunotherapy and before 5th cycle of immunotherapy

q AE/SAE review will be initiated upon ICF obtained. AEs will be identified and collected from time of informed consent to EOT visit.
The investigator should follow up until the event is resolved or when the subject exits the trial.

s Chemotherapy involving 4 cycles of gemcitabine (1000 mg/m^2) and carboplatin (AUC2), with the option of an additional 1 to 2 cycles (ie: up to a total of 6 cycles) if the autologous EBV-specific CTLs are not ready in time for infusion

10. APPENDIX 2 SCHEDULE OF ASSESSMENT (ARM B)

	Pre-Treatment	Chemotherapy				End of Treatment (EOT)	Follow-up ^
	Screening (Baseline)	Cycle 1 to 6			Even Cycles (2, 4, 6)		
	-28 days	Day 1	Day 8	Day 15			
Time- Window	4 weeks from signing informed consent form to 1st chemotherapy dose	1. For Cycle 1 Day 1- within 4 weeks of obtaining informed consent 2. Subsequent cycles Day 1 - ±3 days 3. All cycles Day 8 and 15 - ±3 days 4. Total duration of each cycle should within 25 to 31 days from that cycle day 1 dosing, unless due to treatment delay as per allowed by protocol			After Day 15, before dosing of next cycle	EOT to be done at 30 days (± 5 days) after last dose	Survival status will be followed up every 12 weeks (± 5 days)
Informed Consent	X ##						
Randomization (after eligibility confirmation, before 1st chemotherapy dose)	X [f]						
Pre-Medication		X [c]	X [c]	X [c]			
Chemotherapy (Gemcitabine + Carboplatin)		X [d]	X [e]	X [e]			
Demographics	X						
Medical History and Medication History	X						
Physical Examination [++]	X	X [b]				X	
Vital signs (BP, PR)	X	X [b]				X	
Height	X						
Weight	X	X [b]				X	
ECOG Performance Status	X	X [b]				X	
Urine Pregnancy Test	X						
FBC [+]	X [l]	X [j]	X [j]	X [j]		X	
Serum chemistry [h]	X [l]	X [j]				X	
HBsAg / HIV Antibody or Other Confirmatory Test [m]	X						
ECG	X						
Research blood (At least 10 Arm B patients from sites in Taipei and Taoyuan only)		X[c]			X[n]	X	
Concomitant Medication / Therapy	X	X	X	X	X	X	
AE/SAE evaluation [a]	X	X	X	X	X	X	
CT or MRI for Tumor Response [i]	X [g]				X	X	
QoL		X [c]			X	X	
Survival Status		X	X	X	X	X	X

+	FBC: Hemoglobin, Hematocrit, RBC count, Platelets, Total Leukocyte Count, Neutrophils, Eosinophils, Basophils, Monocytes, Absolute Neutrophil count.
++	Includes, but not limited to the following systems: Head, Eye, Ear, Nose and Throat / Lymph Nodes / Cardiovascular / Thorax / Abdomen / Extremities / Skin and Mucosae / Musculoskeletal / Neurological
##	Written informed consent to be obtained after study has been fully explained to each subject prior to the conduct of any screening procedures or assessments
^	Patients who completed EOT will be followed up on the assessments listed for Follow-up. Patients who commence salvage therapy will exit the study treatment. These patients will be followed up on survival status and initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment.
a	AE/SAE review will be initiated upon ICF obtained. AEs will be identified and collected from time of informed consent to EOT visit. The investigator should follow up until the event is resolved or when the subject exits the trial.
b	To be conducted before the start of each treatment cycle
c	To be conducted before initiating chemotherapy treatment
d	Patients with ANC <1000/mm^3 or Platelet count <100,000/mm^3 or Grade 3 and above AEs, on the first day of a new cycle will delay chemotherapy until recovery. They will have their FBC repeated at weekly intervals until recovery. Patients who experience delays of more than 28 days because of low neutrophil or platelet counts or Grade 3 and above AEs, will be taken off the study treatment. They will undergo EOT visit and followed up on survival status and initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment.
e	Patients with ANC <1000/mm^3 or Platelet count <100,000/mm^3 or Grade 3 and above AEs, during Day 8 or Day 15 chemotherapy will have chemotherapy on that day delayed for up to a week. Should the condition persist past a week, chemotherapy will then be omitted and not replaced.
f	To be conducted prior to first dose of chemotherapy premedication and chemotherapy
g	To be conducted only if last CT or MRI scan is not done within 4 weeks of C1D1
h	Tests include Urea, Serum creatinine, Sodium, Potassium, Chloride, Bicarbonate, Glucose, Bilirubin, Albumin, ALT, AST, ALP, Total protein. Calcium and Magnesium to be performed only at Screening Visit.
i	The method of assessment and the same technique (e.g. CT or MRI) should be used to characterize each identified and reported lesion shall be determined at baseline and remained throughout the study period.
j	To be conducted before starting treatment. Note: FBC, differential counts, Serum Chemistry and research blood within 3 days before the start of each chemotherapy cycle. FBC and differential counts within 3 days before dosing of Day 8 and Day 15 of each chemotherapy
l	FBC and differential counts, Serum Chemistry (results must be within 3 days before starting the 1st chemotherapy for Arm B subject)
m	Status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 4 weeks of screening
n	To be conducted after completion of chemotherapy cycle 2, cycle 4, cycle 5 and cycle 6.

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11. APPENDIX 3 CANDIDATE BIOMARKER LIST

S/N	Biomarker (measure)	Method of ascertainment	Rationale
1	Absolute Lymphocyte Count (ALC)	Blood count	To assess if there are potential pre-chemotherapy simple blood-based biomarkers representing the patient's global immune profile that can predict for a better survival outcome in either arm. In addition, this data can help better understand the impact of chemotherapy on the expansion of EBV-specific CTLs. For example, after four cycles of chemotherapy, will a high (or low) absolute lymphocyte count predict for better survival in either Arm A or Arm B. Can a high NLR or AMC predict for poorer survival as it does in a series of immune-oncology clinical trials across different cancers.
2	Absolute Eosinophil Count (AEC)	Blood count	
3	Absolute Monocyte Count (AMC)	Blood count	
4	Monocyte-Lymphocyte Ratio (MLR)	Blood count	
5	Neutrophil-Lymphocyte Ratio (NLR)	Blood count	
6	Lactate Dehydrogenase (LDH)	Serum test	Patient serum LDH is a surrogate biomarker for tumor burden and a prognostic marker for patient response in some cancers, most notably in lymphoma. There is data for prognostication of LDH in NPC.
7	Circulating EBV DNA load (copies per ml)	Real-time PCR (Technically a test from serum/plasma)	High baseline circulating EBV DNA has been correlated with poor outcomes in many NPC studies both for locoregional disease and advanced disease. This is reported also in a meta-analysis study. It also serves as a surrogate biomarker of response to treatment.
8	Reactivity to LMP2 peptides	ELISpot	This only applies to Arm A. In the single arm Phase 2 trial where 4 cycles of gemcitabine + carboplatin were followed by 6 cycles of EBV CTL, a positive LMP2 specific ELISpot in the CTL product predicted for improved overall survival. In addition, the EBV pepmix will also be studied to see if positive ELISpot assay against pooled peptides can predict for better overall survival.
9	Reactivity to EBV pepmix	ELISpot	

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13. CHANGE HISTORY

Changes incorporated into Version 2.0 of this document.

1. Section 7.5: Rules and processes for IA Decisions

Change: Ceiling for increasing sample size was specified

Rationale: In response to statistical question 1 of FDA comments sent January 11, 2017

2. Section 5.1, 5.2: ITT and MITT population.

Change: MITT population was re-defined.

Rationale: In response to statistical question 2 of FDA comments in January 11, 2017.

3. Section 6.4.2: Handling of missing data for overall survival.

Change: Detailed procedures to minimize the number of subjects with unknown survival status were added. Sample SAS code for Multiple Imputation was added.

Rationale: In response to statistical question 3 of FDA comments in January 11, 2017.

Changes incorporated into Version 3.0 of this document.

1. Section 5.1, Section 5.2: Intent to Treat (ITT) Population and Modified Intent to Treat (MITT) Population

Change: Clarified ITT would be the primary analysis population for efficacy analysis and MITT will be used for supportive analysis

Rationale: In response to FDA's recommendation provided in letter dated 15 February 2017

2. Section 7.2: Interim Efficacy Analysis.

Change: Updated the cutoff for efficacy interim analysis from 50% of subjects accrued for 6 months to 67% of events.

Rationale: To align the original sample size for this event driven study with the plan for the efficacy interim analysis for the sample size re-assessment and to allow more observations to be used for the decision making regarding sample size adjustment by the IDMC at the time of the interim analysis.

3. Section 7.5: Rules and processes for IA Decisions

Change: Ceiling for increasing sample size is clarified and associated effect size intended to be detected is clarified.

Rationale: In response to FDA's comments provided in letter dated 15 February 2017

4. Section 7.6 and 7.7: Data and Metrices Provided to IDMC and Information Provided to Sponsor by IDMC

Change and rationale: New sections added to provide more clarity on the rules of the IA

5. Other editorial and clarifying content changes as needed.

Changes incorporated into Version 4.0 of this document.

1. Section 6.4.2: Handling of Missing Data for Overall Survival

Change: Clarified that subjects with unknown survival status will be censored, instead of having their survival status determined using multiple imputation.

Rationale: In response to FDA's comments provided via email dated 19 October 2017

Changes incorporated into Version 5.0 of this document.

1. Section 2.2: Protocol Objective(s), Section 2.5.2: Secondary Efficacy Endpoints

Change: Inclusion of new secondary objective of "Milestone 2, 3 and 5-year Overall Survival rates".

Rationale: To allow for an alternative assessment of treatment effect in a scenario of non-proportional hazards

2. Section 2.2: Protocol Objective(s)

Change: Inclusion of new secondary objective "Assess the safety and tolerability of both treatments".

Rationale: To align the study objectives with the planned analyses to assess safety.

3. Section 2.2: Protocol Objective(s)

Change: Inclusion of new exploratory objective "Develop a predictive biomarker classifier".

Rationale: To aid in identification of subjects who are more likely to respond to therapy.

4. Section 3: Sample Size Determination, Statistical Power, and Significance level

   Change: Change in target hazard ratio that study aims to detect, together with corresponding updates in the accrual and follow-up times, and explicit statement of trigger for final analysis.

   Rationale: Update of sponsor's study plan.

5. Section 3: Sample Size Determination, Statistical Power, and Significance level

   Change: Deletion of 2nd paragraph "A sample size re-estimation will be performed during the interim analysis as detailed in Section 7.2 of this statistical analysis plan."

   Rationale: The Interim Analysis has been removed for this study, because the survival data observed at the interim are not considered to be sufficiently mature to provide a robust assessment of the probability of success at the final analysis. The target number of events has been increased from 195 to 280 as the expected delay in separation of the survival curves will result in a reduction of power based on the current design to collect 195 events in 330 patients. Optimization of study power in a situation of non-proportional hazards can be accomplished with a longer follow-up time compared to collecting the same number of events from a bigger pool of patients.

6. Section 6.4.3: Handling of Missing Data for other Efficacy Evaluations other than Overall Survival

   Change: Clarified that primary analysis for endpoints of ORR and CBR will be based on the observed data; while a sensitivity analysis will be performed using Non-Responder Imputation.

   Rationale: Other editorial and clarifying content changes as needed.

7. Section 6.4.3: Handling of Missing Data for other Efficacy Evaluations other than Overall Survival

Change: Clarified that subjects with unknown status regarding tumor progression will be censored, instead of having tumor progression status determined using multiple imputation.

Rationale: To align the analysis approach with that of the primary endpoint.

8. Section 6.5.1: Max Combo test

   Change: Deletion of previous analyses based on the MITT population, with new sensitivity analysis taking into consideration the scenario of non-proportional hazards included as a replacement.

   Rationale: To allow recovery of power loss which is implied by design through the application of new techniques that have been proposed to the FDA by other pharmaceutical companies which have conducted immunotherapy trials.

9. Section 6.5.2: Analyses to assess the impact of differential withdrawal of study treatment between arms

   Change: Deletion of previous analyses based on Tipping Point Analysis, with 2 new sensitivity analyses based on looking at prognostic factors of subjects who progressed after 4 cycles of chemotherapy, and censoring of subjects with progressive disease after 4 cycles of chemotherapy proposed.

   Rationale: To address previous comments from the FDA regarding bias arising from differential treatment after 4 cycles of chemotherapy.

10. Section 6.5.3: Association between the number of CTL infusions received and OS

    Change: New analyses to explore whether the efficacy of CTL therapy in Arm A subjects is dependent on the number of infusions received, while adjusting for the possibility of immortal-time bias.

    Rationale: It is of interest to know the extent to which CTL efficacy is dependent on the number of infusions received.

11. Section 6.7: Multiple Testing and Comparisons

    Change: Change in the ordering of the secondary endpoints for closed-testing, taking into consideration the new secondary endpoint proposed.

    Rationale: Based on sponsor's consideration of the relative strengths of each data point.

12. Section 6.8: Covariates

    Change: Clarified that the efficacy analysis of the primary endpoint will be performed with only treatment as a covariate, while covariate-adjusted analysis will be performed as supportive analyses.

    Rationale: Other editorial and clarifying content changes as needed.

13. Section 8.2.1: Analysis of the Primary Endpoint

    Change: Revision of the measures to assess the proportional hazards assumption, as well as additional analyses in-case the proportional hazards assumption is violated.

    Rationale: Based on the recommendations put forth by the cross-pharma working group.

14. Section 8.3: Analysis of Exploratory Objectives

    Change: New section added in to elaborate on analyses that will be undertaken to assess the exploratory objectives. This will include the use of the Cross Validated Adaptive Signature Design (CVASD) in development of a predictive biomarker classifier, as well as other exploratory analyses.

    Rationale: Other editorial and clarifying content changes as needed.

15. Other editorial and clarifying content changes as needed.

Changes incorporated into Version 6.0 of this document.

1. Section 3: Sample Size Determination, Statistical Power, and Significance Level

   Change: Change in target hazard ratio that study aims to detect, together with corresponding updates in the power, accrual and follow-up times.

   Rationale: Update of sponsor's study plan, as communicated to the FDA in response dated 2Feb2019.

2. Section 3: Sample Size Determination, Statistical Power, and Significance Level

   Change: Change in trigger for final analysis to allow for earlier analysis.

   Rationale: Update of sponsor's study plan.

3. Section 5: Analysis Populations

   Change: Deletion of the Modified Intent to Treat (MITT) and Per Protocol analysis

populations in Section 5.2 and 5.3 respectively.

Rationale: Beyond the scope of the planned abbreviated CSR.

4. Section 6.3: Outliers

   Change: Deletion of section from v5.0.

   Rationale: Update of sponsor's study plan

5. Section 6.4: Handling of Missing Data

   Change: Deletion of Sections 6.4.1 Handling of Missing Data for Adverse Events and 6.4.3 Handling of Missing Data for other Efficacy Evaluations other than Overall Survival from v5.0

   Rationale: No imputation will be performed for missing data.

6. Section 6.5.1: Max Combo test

   Change: Deletion of sensitivity analysis.

   Rationale: Beyond the scope of the planned abbreviated CSR.

7. Section 6.3.1: Handling of Missing data for Overall Survival

   Change: Added rule for determination of death date for patients with unknown death date.

   Rationale: In anticipation of such situations given the extended follow-up time.

8. Section 6.4: Definitions of Efficacy and Other Endpoints

   Change: Update in calculations and added text to elaborate on time-to-event endpoints.

   Rationale: Additional clarity in definition of endpoints.

9. Section 7: Summarizing and Tabulating the Collected Data

   Change: ITT and Safety populations to be the basis for analyses of efficacy endpoints.

   Rationale: Update of sponsor's study plan.

10. Section 7.1.11: Treatment Exposure and Compliance

    Change: Additional metrics for analysis of treatment exposure.

    Rationale: Update of sponsor's study plan.

11. Section 7.2.1: Analysis of the Primary Endpoint

    Change: Further details regarding analysis methods to be used.

    Rationale: Additional clarity.

12. Section 7.3: Analysis of Safety Data

    Change: Update in definition of Treatment-emergent adverse events to 8 weeks (56 calendar days) after the last dose of study treatment, inclusive.

Rationale: For consistency with the timing of the End-of-Treatment assessment.

13. Section 8.4.1: Exploratory Analyses using the Cross Validated Adaptive Signature Design

    Change: Section deleted from v5.0.

    Rationale: Analysis approach will be written up in a separate document. Furthermore, this exploratory analysis is beyond the scope of the planned abbreviated CSR.

14. Appendix 3: Candidate Biomarker List

    Change: Revision in list of biomarkers.

    Rationale: Update of sponsor's study plan.

15. Other editorial and clarifying content changes as needed.