Clinical Study Protocol

Study Title:	A Multicenter, Randomized, Open-label, Phase III Clinical Trial of Gemcitabine and Carboplatin followed by Autologous Epstein-Barr Virus-specific Cytotoxic T Cells versus Gemcitabine and Carboplatin as First Line Treatment for Advanced Nasopharyngeal Carcinoma Patients
Study Protocol Number:	FF01
Protocol name:	VANCE
Phase:	III
Sponsor:	Tessa Therapeutics Ltd. 8 Temasek Boulevard, #24-02 Suntec Tower Three Singapore 038988 Telephone: +65 6384 0755 Email: medical@tessatherapeutics.com
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Sponsor Signature Page

Protocol Number: FF01

Protocol Version/Date: 12.0 / 01 May 2020

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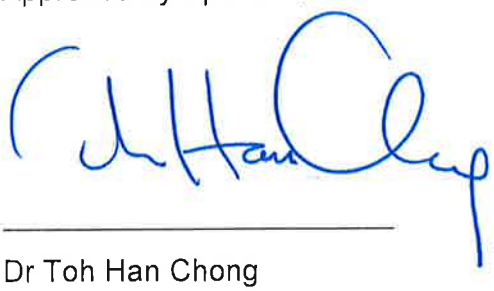
This study will be conducted in compliance with the clinical study protocol, international good clinical practice principles [International Conference on Harmonization (ICH), Good Clinical Practice (GCP)] and regulatory authority requirements.

Approved by Sponsor:



5th MAY 2020

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Investigator Signature Page

Study Acknowledgement

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Investigator Statement

I have read the protocol, including all appendices and I agree that it contains all necessary details for me and my study team to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to conduct the study in accordance with the guidelines of GCP including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)

Name of Institution (Printed)

Address of Institution (Printed)

Signature

Date

Please return a copy of this signature page to Tessa Therapeutics Ltd. or its representing Contract Research Organization (CRO) and retain the original for your site file.

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1 CLINICAL PROTOCOL SYNOPSIS

Study Title	A Multicenter, Randomized, Open-label, Phase III Clinical Trial of Gemcitabine and Carboplatin followed by Autologous Epstein-Barr Virus-specific Cytotoxic T Cells versus Gemcitabine and Carboplatin as First Line Treatment for Advanced Nasopharyngeal Carcinoma Patients
Protocol Number	FF01
Version Number / Date	12.0 / 01 May 2020
Sponsor	Tessa Therapeutics Ltd.
Study Phase	Phase III
Investigational Product (IP)	Autologous Epstein-Barr Virus-specific Cytotoxic T cells (EBV-specific CTLs)
Route of Administration	Intravenous (IV) Injection
Study Centers	30 sites located in Asia and United States
Study Period	3rd Quarter 2014 to 1st Quarter 2023
Objectives	**Primary:** Evaluate the efficacy of EBV-specific CTLs following first line chemotherapy compared to chemotherapy alone in terms of Overall Survival (OS) of patients with advanced nasopharyngeal carcinoma (NPC). **Secondary:** • Evaluate 2, 3 and 5-year OS rates for the two treatment arms. • Assess the Progression Free Survival (PFS) for the two treatment arms. • Compare the Overall Response Rate (ORR), Clinical Benefit Rate (CBR) and Quality of Life (QoL) for the two treatment arms. • Assess the safety of both treatment arms. **Exploratory:** • Demonstrate persistence of EBV-specific immune response in Arm A. • Evaluate biomarkers of response to therapy and in relation to outcome indices. • Explore a predictive biomarker classifier.
Study Design	Multi-center, randomized, open-label, Phase III clinical trial
Number & Type of Subjects	Three hundred thirty (330) patients with metastatic or locally recurrent EBV-positive NPC not amenable to further curative chemoradiation or surgery. Biopsy proven (whether earlier or at diagnosis of *de novo* advanced disease), non-keratinizing and/ or undifferentiated carcinoma of the nasopharynx (EBV-related) patients who have not received first line chemotherapy for the treatment of advanced NPC.

Key Inclusion Criteria	1) Metastatic or locally recurrent EBV-positive, non-keratinizing and/ or undifferentiated NPC* who do not have curative options such as chemo-radiation or surgery **Subjects will be enrolled based on confirmed histology diagnosis of the NPC* 2) Radiologically measurable disease as per RECIST 1.1 3) Human Immunodeficiency Virus (HIV) negative* **Status of HIV must be confirmed via a HIV antibody test or other confirmatory test results available within 4 weeks of screening* 4) Bilirubin < 2x upper limit of normal (ULN) and aspartate aminotransferase (AST), alanine aminotransferase (ALT) < 3x ULN 5) Calculated creatinine clearance (CRCL) ≥ 40 mL/min. Glomerular Filtration Rate (GFR) is calculated based on Cockcroft-Gault method 6) Normal corrected calcium levels 7) Absolute neutrophil count > 1200/mm^3, hemoglobin (Hb) ≥ 10 g/dL and platelets ≥ 100,000/mm^3 8) Male or female 9) Age ≥ 18 years or according to local legal age of consent 10) Eastern Cooperative Oncology Group Performance Scale (ECOG-PS) ≤ 2 11) Written informed consent 12) Life expectancy > 6 months
Exclusion Criteria	1) Severe concomitant illness i.e. chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), active congestive cardiac failure (CCF), active angina pectoris, uncontrolled arrhythmia, uncontrolled hypertension 2) HIV Positive* **Status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 4 weeks of screening* 3) Pregnant or lactating females 4) Refusal of contraception during trial (both male and female patients) 5) Investigational therapy less than one month prior to study entry 6) Pre-existing peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] ≥ 2) 7) Central nervous system metastasis 8) Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors [Ta, Tis and T1] or any cancer curatively treated > 3 years prior to study entry 9) Positive hepatitis B surface antigen (HBsAg) results 10) Known history of hepatitis C and recovery status has not been determined at time of screening 11) Prior anti-cancer treatment for metastatic or locally recurrent disease EXCEPT:

	○ For metastatic or locally recurrent disease, localised palliative radiotherapy is allowed ○ For locally recurrent disease, the following treatments are allowed: • Prior radiotherapy with curative intent • Prior chemo-radiotherapy with curative intent • Adjuvant chemotherapy ○ Prior chemotherapy must be > 6 months before screening 12) Severe intercurrent infections 13) Prior immunotherapy for metastatic or locally recurrent disease ○ The following is allowable: • Adjuvant immunotherapy/ biologics ○ Prior adjuvant immunotherapy/ biologics must be > 6 months before screening
Study Treatment(s)	Eligible subjects will be enrolled and randomized into treatment group Arm A or B in 1:1 ratio using stratified (by country and disease type – metastatic vs locally recurrent) block randomization scheme. **Arm A**: 4 cycles (refer further details in Section 5) of combination IV Gemcitabine (1000 mg/m^2) and IV carboplatin (AUC2) on Days 1, 8, 15 every 28 days, followed sequentially by T cell immunotherapy (2 cycles) of EBV-specific CTLs every 2 weeks, followed by EBV-specific CTL immunotherapy (4 cycles) every 8 weeks after 6 weeks from the second cycle. OR Patients who have not received the first infusion of EBV-specific CTLs, will instead continue to receive a total of 6 cycles combination of Gemcitabine (1000 mg/m^2) and carboplatin (AUC2) on Days 1, 8, 15 every 28 days. **Arm B**: 6 cycles of combination IV gemcitabine (1000 mg/m^2) and IV carboplatin (AUC2) on Days 1, 8, 15 every 28 days.
Duration of Treatment	**Arm A:** Approximately 13 months. (Stage 1: Chemotherapy - 4 to 6 months; Stage 2: EBV-specific CTL immunotherapy – 6 to 7 months) **Arm B:** (Chemotherapy) Approximately 6 months.
Duration of Participation	Up to 4 weeks of screening until death (or lost to follow-up).
Evaluation Criteria and Response	**Overall Survival (OS)** OS is defined as the interval from the day of randomization until death from any cause. Survivors and lost to follow-up patients are censored at the date of last follow-up. **Progression Free Survival (PFS)** PFS is defined as the interval from the day of randomization until radiological disease progression or death from any cause. Patients who receive subsequent anti-cancer therapy will be censored at the date of last tumor assessment prior to first subsequent therapy date. Patients free from disease progression who are alive or lost to follow-up are censored at the date of last tumor assessment.

	RECIST 1.1 Tumor assessment will be performed according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria. All patients who receive at least 1 dose of GC chemotherapy will be evaluable for response. **Overall Response Rate (ORR) and Clinical Benefit Rate (CBR)** Refer to Section 6.2.3 for details • **ORR** is defined as the proportion of individuals who achieve either a CR or PR while on treatment. • **CBR** is defined as the proportion of patients who achieve CR, PR or SD while on treatment. **Quality of Life (QoL)** QoL will be assessed by means of validated questionnaires completed by patients. The EORTC QLQ-C30 [1] will be used. The QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, three symptom scales, a global health status / QoL scale, and 6 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, based on the recommended EORTC procedures [1, 2]. The questionnaire will be available in local languages. Patients on both arms will be asked to complete an interview at selected time points of the study. **Safety** Safety will be assessed throughout the study by the incidence of serious adverse events (SAE), the incidence and severity grade of treatment-emergent adverse events (TEAEs) graded according to NCI-CTCAE version 4.0. Safety will be assessed based on the Safety population, and those who receive at least 1 dose of EBV-specific CTLs. The trial will be conducted according to GCP guidelines and after IRB approval.
Sample Size Rationale	330 patients 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 patients receiving first line conventional chemotherapy at the National Cancer Centre Singapore (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 two arms. An accrual period of 5.5 years, followed by 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.

	No interim analysis will be performed for this study. The final analysis may be triggered when 280 events have been observed 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.
Data Collection	Patient data from this trial will be collected using electronic CRF (eCRF), and/or other traceable and verifiable means. An eCRF will be created for all subjects who provide consent to participate in the trial.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
ABG	Arterial Blood Gas
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMT	Bone Marrow Transplantation
BOR	Best Overall Response
BP	Blood Pressure
BSA	Body Surface Area
CBR	Clinical Benefit Rate
CCF	Congestive Cardiac Failure
CCL22	C-C Motif Chemokine 22
CD-ROM	Compact Disc-Read Only Memory
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRCL	Creatinine Clearance
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Cell
CTLp	Cytotoxic Precursors Cell
CVASD	Cross-Validated Adaptive Signature Design
DLI	Donor Lymphocyte Infusion
DVD-ROM	Digital Versatile Disc-Read Only Memory
EBNA	Epstein-Barr Nuclear Antigen
EBV	Epstein-Barr Virus
EBVST	Epstein-Barr Virus-Specific T cell

Abbreviation or Term	Definition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELISPOT	Enzyme-Linked Immunosorbent Spot
EORTC	European Organization for Research and Treatment of Cancer
EOC	End of Cycle
EOT	End of Treatment
FACS	Fluorescence-Activated Cell Sorting
FBC	Full Blood Count
FU	Flurouracil
GC	Gemcitabine and Carboplatin
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
GVHD	Graft Versus Host Disease
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papilloma Virus
HPVST	Human Papilloma Virus-Specific T Cell
HR	Hazard Ratio
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee (or Independent Ethics Committee)
IFN-γ	Interferon Gamma
Ig	Immunoglobulin
IHD	Ischemic Heart Disease
IL	Interleukin

Abbreviation or Term	Definition
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board (or Independent Review Board)
IRE	Immediately Reportable Event
ITT	Intent-To-Treat
IUD	Intrauterine Device
IV (or iv)	Intravenous
KM	Kaplan Meier
LCL	Lymphoblastoid Cell Line
LD	Largest Diameter
LMP	Latent Membrane Protein
MDSC	Myeloid-Derived Suppressor Cell
MHC	Major Histocompatibility Complex
MITT	Modified Intent-To-Treat
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCCS	National Cancer Centre Singapore
NCI	National Cancer Institute
NMBSCT	Nonmyeloablative Allogenic Blood Stem Cell Transplantation
NPC	Nasopharyngeal Carcinoma
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression Free Survival
PGC	Paclitaxel, Gemcitabine and Carboplatin
PHA	Phytohaemagglutinin
PBMC	Peripheral Blood Mononuclear Cell
PP	Per Protocol
PR	Partial Response
PS	Performance Status
QLQ	Quality of Life Questionnaire

Abbreviation or Term	Definition
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAP	Transporter Associated with Antigen Processing Protein
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
VST	Virus Specific T Cell
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

3 BACKGROUND AND RATIONALE

3.1 Immune Control of EBV Infections

In primary infection, the main route of entry for Epstein-Barr Virus (EBV) is via the oropharyngeal epithelium [3]. Viral replication in these cells subsequently allows infection of B lymphocytes thus resulting in a polyclonal expansion of transformed B cells. These B cells express a number of EBV gene products including nuclear antigen EBNAs 1, 2, 3A, 3B, 3C leader protein and LMP-1, 2A and 2B. In individuals with a normal immune response, tumorigenic/ lymphomagenic outgrowth of infected cells is prevented by the mounting of a complex immune response comprised of human leukocyte antigen (HLA)-restricted EBV-specific CTLs and major histocompatibility complex (MHC)-unrestricted effectors [4].

In individuals with a compromised immune system, EBV is potentially oncogenic. EBV-positive lymphoproliferative disease post-bone marrow transplant that expresses all of the EBV latent antigens can be rapidly fatal [5]. In the immunocompetent host, other EBV-associated tumors have been recognized. However, these express a much more limited range of EBV-associated antigens. For example, malignant Reed Sternberg cells in Hodgkin Disease express latent membrane protein LMP-1, LMP-2 and Epstein-Barr nuclear antigen (EBNA)-1, whereas Burkitt's lymphoma expresses only EBNA-1.

The pattern of EBV gene expression in NPC cells is also more restricted than in either post-transplant lymphoproliferative disease or *in vitro* EBV immortalized B-cell lines [6]. NPC tumors consistently express EBNA-1 but none of the more immunogenic EBNAs. These cells also express LMP-1 on their surface in 65% of the tumors [7]. Although LMP-2 mRNA has been detected, it is unclear whether this viral antigen is expressed [8].

3.2 Nasopharyngeal Carcinoma: Background and Association with EBV

NPC is a malignant disease with a variable range of incidence depending on age, geographical place, race and EBV exposure. It has an annual incidence of nearly 1 case per 100,000 children < 21 years and 0.5 cases per 100,000 adults in the USA [8, 9]. NPC is endemic in southern China and Southeast Asia as there is a high prevalence rate of EBV in the region. It is unique in afflicting southern Chinese individuals in the prime of their economic life. Although NPC is among the more curable cancers, there remains a substantial core of 30% of patients for whom cure is not currently possible.

The etiological factors of endemic NPC include EBV, environmental risk factors and genetic susceptibility [10, 11]. The etiological link between NPC and EBV was first based on serological evidence. Elevated IgG and IgA antibody titers are frequently seen [12]. The association between EBV and NPC was subsequently confirmed by showing that EBV-DNA was present in the NPC tumor cells and that EBV-DNA in NPC biopsy samples is clonal, arising from a single EBV infected cell [13]. EBV has been

detected in virtually all cases of undifferentiated non-keratinizing NPC [8, 14]. On the other hand, squamous cell NPC appears to show a geographical variability with regard to its EBV association with higher EBV positive tumors seen in high incidence areas such as Asia [15]. In addition, squamous cell NPC appears to represent a more heterogeneous group of tumors with other co-factors such as smoking and human papilloma virus (HPV) contributing to the pathogenic process [16, 17]. Nevertheless, there is a strong association of NPC with EBV. Thus, NPC may represent a final common response to several pathological processes that include viral infections, occupational and environmental stimuli with, perhaps, a genetic contribution.

3.3 Host Immune Mechanisms

Both humoral and cell mediated immunity have important roles to play in the control of EBV. EBV-specific CD8+ cytotoxic T-lymphocytes are thought to be the most important defense mechanism against outgrowth of EBV-infected B-cells. These cells recognize peptide fragments, derived from viral antigens, expressed on the surface of antigen presenting cells in association with MHC molecules [18]. Studies using EBV latent proteins expressed in vaccinia constructs have shown that a number of antigens can serve as targets and that the pattern of antigens recognized is dependent on the individual's HLA type [19].

The importance of cytotoxic T-cells is illustrated by the fact that persistent EBV infection is asymptomatic in the majority of virus carriers with a normal immune response. If their immune system becomes compromised, either as a result of disease (eg. Acquired Immune Deficiency Syndrome [AIDS]) or immunosuppressive therapy (eg. post bone marrow transplantation [BMT]), then the probability of developing life threatening EBV-positive lymphoproliferative disease is greatly increased [6, 20]. Patients with inherited disorders of T-cells (eg. X-linked lymphoproliferative disease) have an abnormal response to EBV and present in childhood with either fulminant mononucleosis or EBV-positive lymphoproliferative disease [21]. Patients with NPC may also have suppression of cellular immunity and hence an impaired ability to control viral infection [8].

3.4 Adoptive Immunotherapy in EBV-Associated Malignancies

Further evidence to support the contribution of CTLs to control EBV infection comes from a recent study using EBV-specific gene-modified CTLs to control EBV-positive lymphoproliferative disease post allogeneic BMT [22-24]. EBV specific cytotoxic T-cell lines were prepared from donor leukocytes and infused into 59 allograft recipients as prophylaxis for this complication. Nine of these patients had shown signs of EBV reactivation, with high EBV-DNA levels but, without overt lymphoproliferation. In all of these patients, EBV-DNA levels returned to the control range within 3-4 weeks post immunotherapy although, 3 patients with incipient lymphoma had transient inflammation at the site of disease [25]. Immunotherapy with antigen specific CTLs has also been used therapeutically in 3 patients who developed overt lymphoma [22-24]. Two of these patients responded well and one had biopsy proven accumulation of gene-marked CTL in the disease site. However, this patient who had very bulky

disease also developed a marked inflammatory reaction during therapeutic response illustrating the benefits of a prophylactic approach. The third patient did not respond and died of progressive disease 24 days after CTL therapy. This failure was found to be due to a deletion in EBNA 3B in the tumor cells that removed immunodominant epitopes and thereby caused resistance to killing by the CTLs. Thus, escape mutants may be a problem even when using polyclonal CTL lines, particularly when treating a large tumor load [26].

Having shown that the EBV-positive cells in post-transplant lymphoproliferative disease express a wide range of EBV-encoded antigens are susceptible to immunotherapy, we are now evaluating if the malignant cells of Hodgkin disease and NPC which express a more restricted pattern of antigens, are also targets for this approach.

In a Phase I dose escalation study in Hodgkin disease 8 patients received 2 injections of EBV-specific CTLs [27, 28]. One patient progressed rapidly and came off study within a week. Another patient had erosion of tumor through the Left upper lobe bronchus and died 2 months after EBV-specific CTL infusion. In situ polymerase chain reaction (PCR) for the marker gene revealed gene-marked CTLs within part of the tumor but not at the site of Left upper lobe bronchus erosion. Four patients with aggressive disease at the time of EBV-specific CTL infusion survived for 10 to 12 months and 2 patients were alive for 18 to 24 months after infusion. Gene-marked CTLs were found in peripheral blood up to 9 months following infusion and the number of circulating EBV-specific cytotoxic precursor cells (CTLp) was increased up to 2 logs. This study demonstrates that: 1) immunotherapy with autologous EBV-specific CTLs is safe, 2) gene-marked CTLs persist for up to 5 months after infusion and 3) CTLs can localize to the Hodgkin tumor.

38 advanced NPC patients were treated at the NCCS with combination gemcitabine and carboplatin (GC) for 4 cycles followed sequentially with 6 doses of $1x10^8/m^2$ of EBV-specific T cells [29]. Results are discussed in Section 3.6.

3.5 Mechanisms of Immune Escape in Nasopharyngeal Carcinoma

In order for CD8+ T cells to recognize and subsequently kill virus infected cells, they must recognize short peptides, derived from virus-associated antigens, in conjunction with specific MHC class I molecules on the surface of antigen-presenting cells. Virus infected cells have the ability to persist by escaping this CTL mediated control. The exact mechanism whereby this occurs in EBV infected cells, is unknown but several possibilities exist: 1) absence/down regulation of MHC molecules, 2) absence/ down regulation of transporter proteins (e.g. TAP-1 and TAP-2), or 3) absence or low expression of cellular adhesion and co-stimulatory molecules. In NPC, Hodgkin disease and Burkitt's lymphoma, not all of the viral antigens are expressed. Therefore, down-regulation of these viral antigens represents a fourth mechanism whereby infected cells can escape an effective immune response.

Studies of several NPC tumor cell lines have demonstrated normal expression of MHC class I molecules. In contrast to the reported deficiency of TAP-transporters in Burkitt's lymphoma, NPC tumor cells express normal levels of the peptide transporters TAP1 and TAP2. In addition, the NPC tumor cells express the regulatory molecules CD40, CD70 and CD80/ CD86, which allows interaction with antigen-specific CTLs [30]. Finally, NPC tumors cells have been shown to be capable of processing and presenting endogenously synthesized protein to HLA class I-restricted CTL clones [31, 32].

Why is it however, that NPC tumors *in vivo* can apparently grow in the face of an otherwise intact EBV specific immunity? Firstly, the restriction of the EBV antigens (type II latency) expressed on the tumor cell surface is an important strategy by which the immune system is evaded as explained below. In addition, NPC and Hodgkin disease are unusual in that in each case, the bulk of the tumor is composed of normal cells (lymphoid and other inflammatory cells) which are intimately admixed with the tumor cells, forming the so called lymphoid stroma [8]. It is therefore appears that the NPC and Hodgkin tumor cells are able to actively modulate their microenvironment, resulting in an ineffective immune response [8].

As mentioned previously, EBV-positive NPC cells regularly express the nuclear antigen EBNA1 and a subset of tumors also appear to be latent membrane protein LMP1 positive [33]. Transcriptional analysis has shown expression of LMP2 mRNA in the majority of tumor biopsies [7]. In addition, transcription of the BARF0 gene has been detected in NPC cells [34]. In healthy EBV+ donors, CTL responses against an HLA-A2 restricted epitope encoded by the BARF0 gene were reported [35]. In the peripheral blood of NPC patients, LMP2-specific CTLs were demonstrated [32]. EBV-infected NPC cells do not express any other nuclear antigens than EBNA1 that are known to contain important CTL epitopes. In vitro studies have failed to isolate CD8+ CTLs specific for EBNA-1. Moreover, EBNA-1 contains a glycine-alanine repeat domain that prevents its processing via the HLA class I pathway and therefore does not represent a potential target epitope [36].

3.6 Rationale for Current Protocol and Results of Previous Phase II Trial

In our recently completed single arm Phase II trial of first-line GC for 4 cycles followed by autologous EBV-specific CTLs in 38 patients, we showed that such an approach is feasible and has comparably very good efficacy with a favorable toxicity profile [29] and has achieved favorable survival outcome for patients with advanced stage disease. It is only logical that a randomized trial be carried out to accurately assess if combined gemcitabine-carboplatin followed by adoptive T cell therapy would improve clinical outcome for patients with advanced NPC.

Thirty-five patients received both chemotherapy and T cell infusion and all 35 experienced clinical benefit. Twenty-four (68.6%) patients completed the entire treatment. The median number of administered EBV-specific CTL doses was 6 and the median total EBV-specific CTL dose was 10.2 $x10^8$ cells (range 7.8 to 12.0 $x10^8$ cells). The main reason for failure to complete the 6 doses of EBV-specific CTL therapy

was disease progression. For 3 patients, EBV-specific CTLs were not initiated due to rapid disease progression or death.

The median follow-up of the 35 patients who received chemotherapy and EBV-specific CTL was 29.9 months (range: 5.1 – 47.7).

Out of 38 patients who received chemotherapy, 3 patients (7.9%) had a CR, 21 patients (55.3%) had PR and 12 patients (31.6%) had SD as best response to chemotherapy, leading to a response rate of 63.2% and a CBR of 94.7% One patient (2.6%) progressed on chemotherapy and one (2.6%) was not evaluable (Table 1**Error! Reference source not found.**).

Table 1: Response and Clinical Benefit Rate

	Chemotherapy Phase (n = 38)		Immunotherapy Phase (n = 35)		For Combined Chemo-Immunotherapy (n = 35)	
	No	%	No	%	No	%
Best Overall Response (BOR)						
CR	3	7.9	2	5.7	3	8.6
PR	21	55.3	13	37.1	22	62.9
SD	12	31.6	7	20.0	10	28.6
PD	1	2.6	11	31.4	0	-
Not assessed	1	2.6	2	5.7	0	-
Response Rate (RR)						
No of patients with BOR = CR/PR	24		15		25	
RR, %	63.2		42.9		71.4	
(95% CI)	(46.0 – 78.2)		(26.3 – 60.7)		(53.7 – 85.4)	
Clinical Benefit Rate (CBR)						
No of patients with BOR = CR/PR/SD	36		22		35	
CBR, %	94.7		62.9		100.0	
(95% CI)	(82.3 – 99.4)		(44.9 – 78.5)		(90.0, 100.0)*	

BOR: Best Overall Response; CBR: Clinical Benefit Rate; CI: Confidence Interval; CR: Complete Response; PR: Partial Response; PD: Progressive Disease; RR: Response Rate; SD: Stable Disease. *One-sided 97.5% CI.

Response to immunotherapy was determined by comparing pre- and post-EBV-specific CTLs imaging studies with the new tumor baseline established after the completion of chemotherapy. Out of 35 patients who received EBV-specific CTLs post chemotherapy, 2 patients remained in CR (5.7%), 13 patients had a PR (31.7%) and 7 patients (20%) experienced SD as best response to the EBV-specific CTL therapy, leading to an ORR of 42.9% and a CBR of 62.9% to the EBV-specific CTL.

This combined chemotherapy and EBV-specific CTL study has achieved, 1-, 2- and 3-year overall survival rates of 77.1% (95% CI: 59.5%-87.9%), 62.9% (95%CI: 44.8%-76.5%) and 37.1% (95%CI: 21.1%-52.7%) respectively (Table 2). The median overall

PFS was 7.6 months (95%CI: 7.4-8.4 months) with 25.7% of patients being free of disease progression at the 1-year mark. The median PFS for the EBV-specific CTL immunotherapy phase was 3.7 months (95%CI: 2.4-4.0 months, range 2.0-35.3 months). Five patients had prolonged disease stabilization of more than 52 weeks after the first EBV-specific CTL infusion. Furthermore, 5 patients had not required systemic chemotherapy for more than 34 months since the start of the EBV-specific CTL therapy.

Table 2: Overall Survival of Patients on GC-CTL, PGC-5FU, and PGC Clinical Trials

	GC-CTL^ (n = 35)	GC-CTL# (n = 38)	PGC-5FU* (n = 28)	PGC** (n = 32)	P-value			
	[A] Patients who received CTL	[B] All Patients	[C] All Patients	[D] All Patients	[A] vs [C]	[A] vs [D]	[B] vs [C]	[B] vs [D]
Follow-up, months								
Median	29.9	26.6	21.4	17.7	0.191	0.040	0.472	0.162
Range	5.1 – 47.7	2.0 – 47.7	1.8 – 42.4	4.4 – 43.9	-	-	-	-
Overall Survival (OS)								
No. of events / patients	23/35	26/38	21/28*	26/32**	0.268	0.037	0.485	0.103
Median OS, months	29.9	26.6	21.4	18.3				
(95% CI)	(20.83, 39.29)	(18.56, 34.37)	(14.09, 30.03)	(13.21, 23.06)				
1-year OS, %	77.1	71.1	75.0	81.3				
(95% CI)	(59.46, 87.85)	(53.86, 82.80)	(54.61, 87.21)	(62.95, 91.11)				
2-year OS, %	62.9	57.9	42.9	29.5				
(95% CI)	(44.77, 76.47)	(40.76, 71.69)	(24.57, 59.96)	(14.84, 45.85)				
3-year OS, %	37.1	34.2	25.0	16.4				
(95% CI)	(21.10, 52.7)	(19.8, 49.1)	(9.85, 43.64)	(6.00, 31.30)				

CI: confidence interval; CTL: cytotoxic T cells; GC: Gemcitabine and Carboplatin; 5-FU: 5-flurouracil; OS: overall survival; PGC: Paclitaxel, Gemcitabine and Carboplatin.

^ 35 patients who received both GC and EBV-specific CTL "per-protocol".

38 patients analyzed as "intention-to-treat".

* OS for the PCG+5FU trial are consistent with previously reported.

** OS for the PCG trial is slightly different from previously reported. Our results include additional follow-up data collected as of 2007 which contained 11 more deaths as compared with 15 deaths reported in the original publication.

3.7 Dose Rationale for Chemotherapy and Immunotherapy

3.7.1 Outcome Comparisons with Other Trials

Exploratory analysis was performed to compare survival outcomes between this trial and two independent first-line GC-based chemotherapy trials performed at the NCCS. Although non-randomized, the patient characteristics across these 3 trials were

broadly similar. Using individualized patient data, survival was analyzed on both an "intention-to-treat" and "per-protocol" basis and the data is summarized in Table 2. Patients who received per-protocol GC-EBV-specific CTL had an improved median OS of 29.9 months, as compared to 18.3 months for Paclitaxel, Gemcitabine and Carboplatin (PGC) (p=0.037) and 21.4 months for PGC-5-Flourouracil (FU) (p=0.191). Two-year OS rates were 62.9%, 42.9% and 29.5%; and the 3-year OS rates were 37.1%, 25% and 16.4% for the GC-EBV-specific CTL, PGC-5FU and the PGC trials respectively, strongly suggesting a benefit of the use of combined chemotherapy-EBV-specific CTL therapy. Furthermore, our outcomes compare favorably to previous clinical trial report by BB Ma et al [37] using gemcitabine and Ngan et al [38] using GC against advanced NPC, with OS of 15.0 months and 1-year survival rate of 62%. Although the addition of 5-FU to PGC yielded a slightly improved overall survival of 22 months and a 2-year survival rate of 43%, patients experienced significant Grade 3/4 neutropenia, anemia and thrombocytopenia, although there was no treatment-related mortality. In contrast, we did not observe any toxicity effects following the inclusion of adoptive T cell immunotherapy in our single arm Phase II clinical trial. Following completion of the 6 x EBV-specific CTL infusions in our Phase II study, 15 patients (43%) further responded and 22 patients (63%) experienced clinical benefit when using post-GC as the new baseline for assessing clinical responses. A total of 249 paired data points of EBV-DNA levels and tumor diameter from 35 patients who received chemo-immunotherapy were analyzed. Plasma EBV-DNA load significantly correlated with tumor diameter (correlation coefficient: 0.696; 95% CI, 0.617 – 0.774; $p < 0.001$) above a threshold of an EBV-DNA load of ~150 copies/mL. Cox regression analysis revealed that for every 2-fold increase in EBV-DNA load at baseline, the mortality hazard increased by ~28% (HR 1.28; p=0.004). In contrast, no correlation was observed between baseline EBV-DNA levels and treatment response.

Based on ELISPOT analysis, 25 patients received CTL products containing T cells specific for the EBV latent antigen LMP2 expressed in NPC tumors. These patients had significant improved OS compared to those (n=9) who received CTL products lacking LMP2 specificity. [Hazard ratio (HR) = 0.35; 95% CI, 0.14 – 0.81; p = 0.012].

Analysis on cytokine levels in patient serum was also performed using the human multiplex-25 bead array assay kit. Of all the cytokines and chemokines evaluated, only CCL20 (MIP3alpha) was inversely associated with long term survival (p=0.035). In contrast, circulating interferon (IFN)-γ levels showed significant positive correlation with both 2-year survival and long-term survival (p=0.013 and 0.002 respectively). Overall, these results suggest that the quality of systemic immune polarization at key time points post infusion may correlate with long term outcome for patients undergoing combination T cell therapy for NPC.

We hypothesize that this combined first line chemo-immunotherapy strategy will produce superior OS, improved PFS, better clinical benefit and better quality of life compared to conventional chemotherapy treatment. In this study, we propose to evaluate, in an intent-to-treat, unblinded, Phase III randomized setting, the efficacy of

adoptive autologous EBV-specific CTL following upfront platinum-based chemotherapy in patients with advanced NPC.

We and our collaborators at Baylor College of Medicine, Houston, Texas, have demonstrated the feasibility of CTL therapy for EBV-positive NPC in small series of immunocompetent NPC patients, providing evidence of anti-tumor activity of EBV-specific CTLs in this patient population. We previously proposed that the anti-tumor efficacy of CTLs can potentially be improved by decreasing the tumor burden and possibly creating immunological space and reducing the inhibitory microenvironment with GC, a common first line combination chemotherapy for advanced NPC. In addition, preclinical studies and early clinical studies indicate that gemcitabine might also augment anti-tumor immunity by reducing myeloid derived suppressor cells, expand effector T-cells, increase CD4+ and CD8+ T-cell infiltration into tumors, release tumor antigens from the stroma to further activate CTL response and enhance tumor antigen cross-presentation [19].

Furthermore, the researchers at the NCCS have established translational and clinical expertise and experience in cell and immunotherapy for NPC and other cancers. In chemorefractory, heavily pre-treated and incurable NPC, we have shown in a first-in-man clinical trial that nonmyeloablative allogeneic blood stem cell transplantation (NMBSCT) with or without donor lymphocyte infusion (DLI) in patients with chemorefractory (median of more than two prior lines of chemotherapy received) metastatic NPC achieved an overall response rate of 40%, and an overall disease-control rate of over 70%, with a more than acceptable side effect profile by international benchmarks. Our results compare very favorably with 2nd line cytotoxic treatments that typically achieve response rates of 10% to 20%.

In spite of these compelling results, limitations in successfully identifying suitable HLA-matched or one-antigen mismatched sibling donors (only 25-50% succeed) for NMBSCT, and potential adverse side effects as for any allograft transplant, have led us to now consider autologous adoptive CTL therapy targeted at EBV tumor-associated antigens as treatment for advanced NPC.

3.7.2 Risks and Benefits of Administrating EBV Specific CTLs

3.7.2.1 Risks

Over 70 patients have been treated on similar CTL protocols at the Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas, in which allogeneic EBV-specific CTLs were administered after BMT or autologous CTLs were administered to patients with Hodgkin disease or severe chronic EBV infection [22-24, 28]. The main complication observed has been inflammatory reaction at tumor sites in patients with post-transplant lymphoma and active disease at the time of CTL administration. None of the patients in the post-transplant lymphoma protocol who developed this complication had long-term sequelae. No increased incidence of *de novo* Graft Versus Host Disease (GVHD) was observed. Should inflammation reaction occur, investigators should provide appropriate treatment (e.g. steroids, supportive care or

oxygen) to the patient as needed. Patients should also be reviewed more closely (e.g. earlier clinic visit than schedule if applicable).

In this Phase III clinical study, the CTLs will be derived from the patients' own autologous blood. Hence the risks of administration will be minimal as autoreactive cells will be absent. All CTLs will be tested for their ability to kill patient-derived phytohaemagglutinin (PHA) stimulated lymphoblasts, which would indicate autoreactivity. Lines with such activity will be eliminated from the study. We think that the likelihood of an inflammatory response is less in this study as the tumor cells are less immunogenic. Moreover, the EBV genome positive malignant cells comprise only a small percentage of overall cells compared to post transplant EBV lymphoma where all cells in the tumor are EBV positive.

Another potential hazard is the infusion of EBV-transformed B cells, which have been co-cultured with the CTL during generation of T cell lines. This is unlikely to constitute an additional risk to the patient because the lymphoblastoid cells have been irradiated with 60-100 Gy and co-cultured with virus specific CTLs. The risk of introduction of infectious EBV into the patient is eliminated by the culture of lymphoblastoid cell lines (LCLs) for at least 14 days with Acyclovir prior to use. Previous Phase II study has already shown that this abrogates the release of infectious virus from LCLs during the period of co-culture. Finally, the levels of EBV-DNA in peripheral blood will be monitored by PCR and copy number monitored, before and after CTL infusions.

3.7.2.2 Benefits

As the benefit information of chemotherapy with immunotherapy is still very limited, there is no assurance subjects will benefit from this study. However, the data from this study will contribute to the medical knowledge about the use of chemotherapy combined with immunotherapy as a possible treatment for advanced NPC and help advanced NPC in the future.

3.8 Previous Results

In an early phase dose finding study at Baylor College of Medicine, Houston, Texas, 10 patients with NPC were enrolled on a Phase I/II dose finding and efficacy study. Apart from one patient on dose level 1 who had increased swelling due to disease progression, there have been no adverse effects of EBV-specific CTL infusion. The 4 high risk patients treated on an adjuvant basis remained in remission 19 to 27 months post EBV-specific CTL. Of 6 patients with metastatic disease, 2 had CR and remained in remission over 11 to 23 months, one had a very good PR for 12 months, and one had SD for more than 14 months. Two patients had disease progression with therapy [39].

3.9 Rationale for Immunological Assessment & Biomarker Analyses

While studies of Virus specific-T cells (VSTs) in the clinical setting have been limited, one Phase I trial using Human Papilloma Virus-Specific T Cells (HPVSTs) against cervical cancer, showed an increased IFNγ response of the HPVSTs, which correlated

with favorable outcome [40]. Another Phase II clinical trial, utilizing Epstein–Barr Virus Specific-T Cells (EBVSTs) against NPC, also revealed higher serum IFNγ levels correlating with improved survival. In addition, this trial also noted an association with decreased viral load with increased overall survival, again demonstrating the utility of applying more than one biomarker to discretize patients [29].

Taken together, these reports indicate that measurement of multiple parameters that encompass both the positive impact of immunotherapy and the negative impact of immune suppression by the tumor will need to be accounted for. For our clinical trial we will explore whether those patients in the chemotherapy arm alone, will experience an increase in EBV viral load, as well as an increase in inhibitory leukocyte cell numbers, which can include regulatory T cells, monocytic and granulocytic myeloid-derived suppressor cells (MDSCs) and their associated immunoinhibitory proteins compared to those in the chemotherapy-EBVST arm [29, 41-46].

These biomarkers will then be correlated to the clinical outcomes as measured by OS, PFS, ORR, and CBR.

4 STUDY OBJECTIVES

4.1 Primary Objectives

- Assess the efficacy of EBV-specific CTL following first line chemotherapy compared to chemotherapy alone in terms of Overall Survival (OS) of patients with advanced NPC.

4.2 Secondary Objectives

- Evaluate 2, 3 and 5-year OS rates of the two treatment arms.
- Assess the Progression Free Survival (PFS) for the two treatment arms.
- Compare the Overall Response Rate (ORR), Clinical Benefit Rate (CBR) and Quality of Life (QoL) for the two treatment arms.
- Assess the safety of both treatment arms.

4.3 Exploratory Objectives

- Evaluate persistence of EBV-specific immune response.
- Evaluate biomarkers of response to therapy and in relation to outcome indices.
- Explore a predictive biomarker classifier.

5 STUDY DESIGN

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

Patients with metastatic or locally recurrent EBV-positive NPC not amenable to further curative chemoradiation or surgery are eligible for this study. Eligible patients 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.

Patients will be randomized after their eligibility status has been fully determined and informed consent has been obtained. Patients will be randomly allocated to receive 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).

Arm A consists of 2 stages:

- 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 EOC4 and patient's EOC4 evaluation scan shows CR, PR, SD
- Stage 2: Immunotherapy involving 6 cycles of EBV-specific CTL infusion (1x10^8 cells/m^2)

After randomization, patients 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 to 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 patient's evaluation scan after the 4th cycle of chemotherapy shows CR, PR, SD[OBJ], 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 (see Section 5.6.5 and Table 3).

An evaluation computed tomography (CT)/ magnetic resonance imagining (MRI) scan will be performed before the 3rd cycle of chemotherapy. The response to chemotherapy will be noted. Patients who are assessed as Progressive Disease (PD) on imaging assessment may decide to seek alternative treatment based on the attending clinician's advice.

An Evaluation CT/MRI scan will be repeated after the 4th cycle of chemotherapy [end of cycle 4 (EOC4) scan], or before commencement of EBV-specific CTL infusions.

Refer to Section 5.1 study schema for further details.

Patients will be assessed by CT/ MRI scan for response to immunotherapy approximately 7 weeks after the first EBV-specific CTL infusion. Evaluation CT/MRI scans will initially be repeated approximately 7 weeks after receipt of each maintenance EBV-specific CTL infusion. Following the end of treatment, patients will be followed up on survival status [Refer Schedule of Assessment (Arm A) Appendix 1 table].

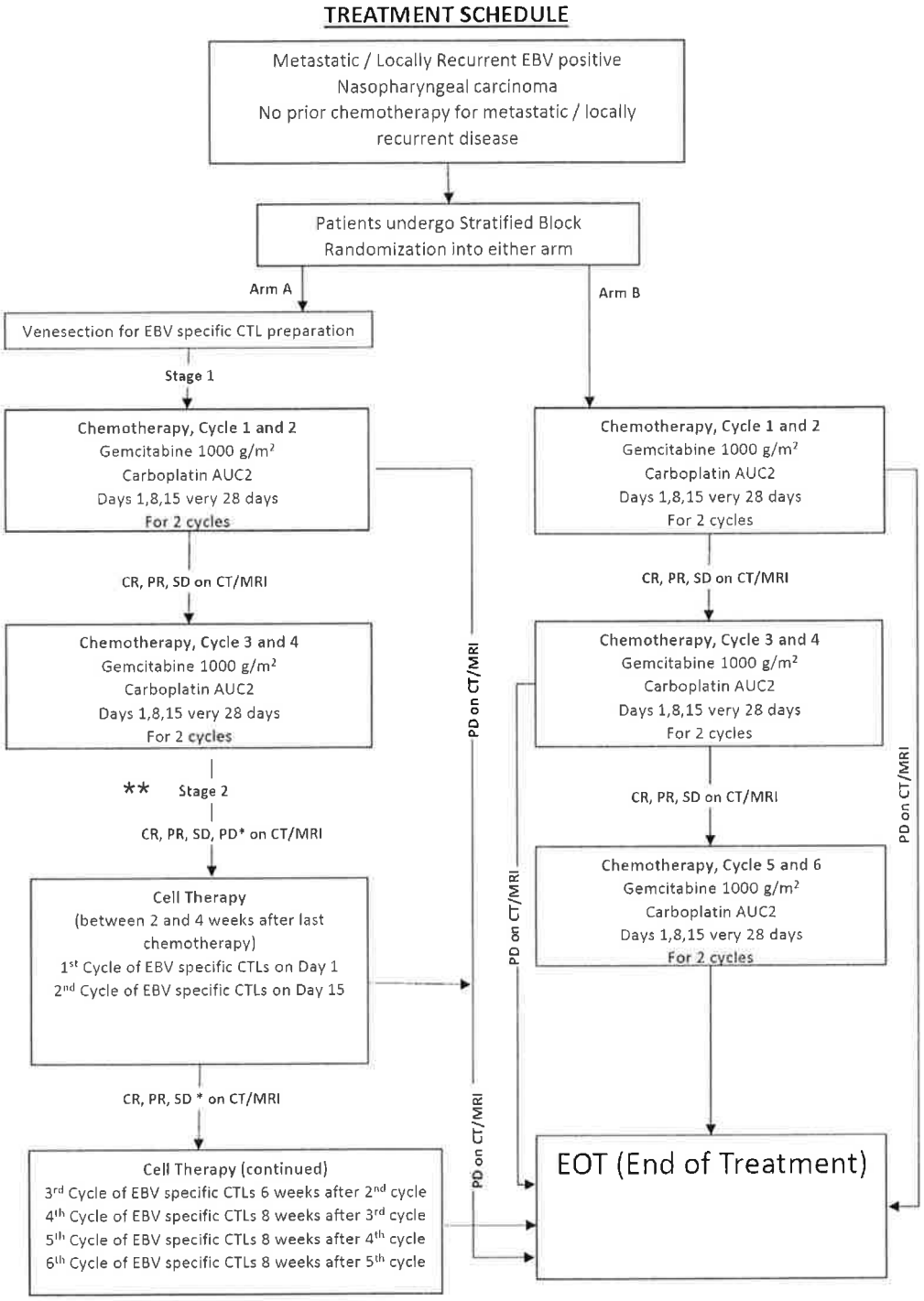
Patients who demonstrate clinical benefit (CR, PR, SD) to the first 2 cycles of immunotherapy will continue with immunotherapy. Patients with asymptomatic PD on imaging assessment can continue with EBV-specific CTL based on the attending clinician's discretion. This is based on the known biological and clinical fact that optimal immunotherapy responses may be delayed and are frequency-dependent.

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

Within 4 weeks of obtaining informed consent, patients will commence combination gemcitabine and carboplatin chemotherapy for a total of 6 cycles. Evaluation CT/MRI scans 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). Patients who are assessed as PD on imaging assessment may decide to seek alternative treatment based on the attending clinician's advice.

An evaluation CT/MRI scan will initially be repeated every 8 weeks during study treatment and at EOT visit. Following EOT, survival status will be followed up. [Refer Schedule of Assessment (Arm B) Appendix 2 table].

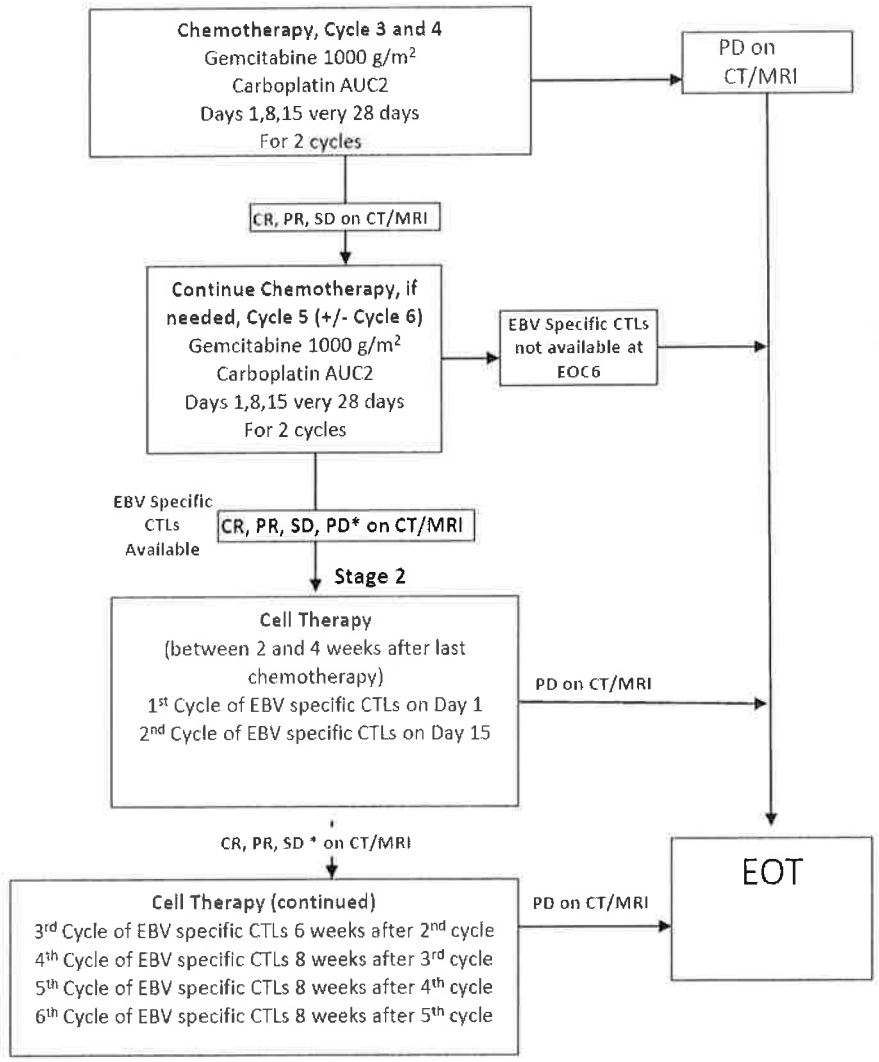
5.1 Study Schema



* 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.

5.2 Selection of Study Population

The study population for this study will be metastatic or locally recurrent EBV-positive NPC not amenable to further curative chemoradiation or surgery. These subjects shall be 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.

5.3 Consent and Screening

Patients will be referred by their primary physicians in consideration for this study. A screening log must be kept of all patients considered for the study and subsequently excluded. The reason for exclusion must be also recorded.

Patients who are referred for this trial will have a counseling session with the clinical trial team to explain the rationale, benefits and potential risks in participating in this clinical trial. The chemotherapy / CTL infusion procedure as well as the possible side effects will be explained to the patient. It will be pointed out specifically that EBV-specific CTL therapy is still considered experimental, but that preliminary data has suggested efficacy. Patients will be informed that they retain the right to withdraw from the study at any time. The patient will be thoroughly evaluated, a detailed history and physical examination and a series of studies to confirm medical eligibility. Treatment recommendations and alternatives will then be discussed thoroughly with patient and family.

All patients must sign a document of informed consent consistent with local institutional guidelines stating that they are aware of the investigational nature of this protocol and of the possible side effects of treatment. Further, patients must be informed that no efficacy of this therapy is guaranteed, and that unforeseen toxicities may occur. Patients have the right to withdraw from this protocol at any time. No patient will be accepted for treatment without such a document signed by him or his legal guardian. Full confidentiality of patients and patient records will be provided according to institutional guidelines.

All study related costs will be borne by the sponsor [e.g. manufacturing and production of CTL therapy, bloods for Immune function assays, cytotoxicity assays, EBV DNA PCR and fluorescence-activated cell sorting (FACS) analysis etc.].

The sponsor will purchase clinical trial insurance for this study. Compensation for research-related injury shall be paid by the study sponsor according to the applicable local regulations. Compensation may also be considered on a case-by-case basis for unexpected injuries due to non-negligent causes. There will be no compensation for the expected injuries or conditions due to the chemotherapy or patients' diseases.

5.4 Eligibility Criteria

5.4.1 Inclusion Criteria

1) Metastatic or locally recurrent EBV-positive, non-keratinizing and/ or undifferentiated NPC* who do not have curative options such as chemo-radiation or surgery
   **Subjects will be enrolled based on confirmed histology diagnosis of the NPC*
2) Radiologically measurable disease as per RECIST 1.1
3) Human immunodeficiency virus (HIV) negative*

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

4) Bilirubin < 2 x upper limit of normal (ULN) and aspartate aminotransferase (AST), alanine aminotransferase (ALT) < 3 x ULN

5) Calculated creatinine clearance (CRCL) ≥ 40 mL/min. Calculated creatinine clearance (CRCL) ≥ 40 mL/min. GFR is calculated based on Cockcroft-Gault method.

6) Normal corrected calcium levels

7) Absolute neutrophil count > 1200/mm^3, hemoglobin (Hb) ≥ 10 g/dL and platelets ≥ 100,000/mm^3

8) Male or female

9) Age ≥ 18 years or according to local legal age of consent

10) Eastern Cooperative Oncology Group-Performance Scale (ECOG-PS) ≤ 2

11) Written informed consent

12) Life expectancy > 6 months

5.4.2 Exclusion Criteria

1) Severe concomitant illness i.e. chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), active congestive cardiac failure (CCF), active angina pectoris, uncontrolled arrhythmia, uncontrolled hypertension

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

3) Pregnant or lactating females

4) Refuse of use of contraception during trial (both male and female patients)

5) Investigational therapy less than one month prior to study entry

6) Pre-existing peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] ≥ 2)

7) Central nervous system metastasis

8) Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors [Ta, Tis and T1] or any cancer curatively treated > 3 years prior to study entry

9) Positive hepatitis B surface antigen (HBsAg results

10) Known history of hepatitis C and recovery status has not been determined at time of screening

11) Prior anti-cancer treatment for metastatic or locally recurrent disease, EXCEPT:

- For metastatic or locally recurrent disease, localised palliative radiotherapy is allowed
- For locally recurrent disease, the following treatments are allowed:
  - Prior radiotherapy with curative intent
  - Prior chemo-radiotherapy with curative intent
  - Adjuvant chemotherapy
- Prior chemotherapy must be > 6 months before screening

12) Severe intercurrent infections

13) Prior immunotherapy for metastatic or locally recurrent disease
    - The following is allowable:
      - Adjuvant immunotherapy/ biologics
    - Prior adjuvant immunotherapy/ biologics must be > 6 months before screening

5.5 Randomization and Treatment Procedures

Stratified block randomization will be carried out on the following factors:

- Country
- Disease type: metastatic versus recurrent

Within each stratum, patients will be allocated with equal probability to either Arm A (GC and EBV-specific CTLs) or Arm B (GC alone). Blocks of consecutive patients will be generated for each stratum by the statisticians, and the block length will be blinded to all other research personnel until trial closure.

When a patient gives written informed consent and meets all the eligibility criteria, the investigator or authorized site personnel will randomize this patient via the web randomization program. A subject number and treatment arm will be assigned to the patient by the randomization program.

As this is an open-label randomization study, no emergency unblinding will be required.

5.6 Treatment Preparation and Administration

5.6.1 EBV Transformed Lymphoblastoid Cell Line Preparation (EBV-LCL) (Arm A)

After randomization, the patient on Arm A, will provide approximately 300 mL (up to 350mL) of peripheral blood. Hb should be tested within 7 days of venesection and must be ≥ 10 g/dL. Patients who have Hb < 10 g/dL before venesection of approximately 300mL of peripheral blood will be transfused with red blood cells. These patients may additionally be given erythropoietin subcutaneously (to be considered

only as per the recommendations, warnings on packaging inserts for the intended population). For these patients, investigators shall monitor red blood cell levels (hemoglobin) and to adjust the erythropoietin dose to maintain the lowest hemoglobin level needed to avoid the need for additional blood transfusions. Investigators and patients should also carefully weigh the risks of erythropoietin (e.g. as per the black boxed warnings) against transfusion risks. The blood drawn should be sent under ambient conditions (15 - 25°C) and processed within 48 hours. Part of the 300 mL of peripheral blood will be used for the establishment of an EBV-LCL by infection with virus produced from a clinical grade marmoset B lymphoblastoid cell line (B95-8 master cell line). Once the EBV-LCLs are established, the CTL line will be prepared by co-cultivation of the irradiated EBV-LCL with patient peripheral blood mononuclear cells (PBMCs). CTLs will take approximately 18 weeks to be ready for infusion from the start of processing.

5.6.2 Cytotoxic T Cell Line Preparation

A proportion of peripheral blood will be used to generate EBV-specific CTLs as described by Lapteva N *et al* using gas permeable flasks [47]. The phenotypic markers of the CTL line will be characterized via immune assays, including those expressed in EB virus-positive NPC tumor cells; EBNA-1, LMP-1 and LMP-2a or pentamer reagents. After establishment, the CTL lines will be checked for identity and microbiological culture and cryopreserved prior to administration [23, 48].

As per previous experience, there may be chances that the production of CTLs may fail or the yield may be insufficient to generate sufficient CTLs for complete treatment cycles.

Should such incidents occur, additional blood of 200 mL (up to maximum 250 ml) will need to be collected from those patient(s)*. If cell yield is still not sufficient after this additional blood is collected, the patient will be withdrawn from the study treatment, undergo EOT visit and followed-up on survival status. Subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment should be recorded.

* *The additional blood collection might occur during chemotherapy or CTL infusion phase. There should be at least a 14 days interval from the last dose of chemotherapy or 24 hours after EBV-specific CTL infusion, 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.*

5.6.3 Stage 1 – Chemotherapy

After venesection of blood for CTLs, the patient will begin the first stage of therapy. Gemcitabine 1000 mg/m2 and carboplatin AUC 2 will be administered on a Day 1, 8 and 15 schedule every 4 weeks. Pre-medication will consist of dexamethasone (or equivalent) and Granisetron (or equivalent). Patients will receive 4 cycles of

chemotherapy (up to a maximum of 6 cycles) (refer to Section 5). For carboplatin dosage calculation, Calvert's formula will be used. Note the GFR used in Calvert's formula to calculate AUC-based dosing should not exceed 125 mL/min [49].

5.6.4 Chemotherapy Treatment Modification/Omission/Termination

Patients who have previously received extensive spinal or pelvic irradiation should have the first dose of chemotherapy reduced by 20% to 30% in anticipation of poor bone marrow reserve.

Patients with ANC < 1000/mm3 or platelet count < 100,000/mm3 or Grade 3 and above AEs, on the first day of a new cycle will delay chemotherapy until recovery. They will have their full blood count (FBC) evaluated to confirm recovery status. 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.

Patients with ANC < 1000/mm3 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.

Patients who are unable to tolerate chemotherapy side effects, or who experience frequent dose delays /omissions may have the dosage of either gemcitabine or carboplatin or both chemotherapies reduced by up to 30%. Dose reductions and their reason will be clearly documented in the case-notes.

Any patients who have to suspend chemotherapy treatment (despite reduction) for more than 28 days, due to Grade 3 and above AEs or any other reason, will be discontinued from further chemotherapy. These patients will undergo EOT visit and be followed up on survival status. Subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment should be recorded.

Patients who progress after 2 cycles of chemotherapy may be considered for salvage therapy. Patients who experience rapid progression and who commence salvage therapy will exit the study treatment. These patients will be followed up on survival status. Subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment should be recorded.

In total, 4 cycles of chemotherapy are planned in Arm A. *However, Investigators may consider adding an additional 1 to 2 cycles of chemotherapy (i.e. up to a total of 6 cycles) when the EBV-specific CTLs are not ready for infusion after EOC4 and patient's EOC4 evaluation scan shows CR, PR or SD (also refer Section 5 - Study Design).*

5.6.5 Stage 2 - Immunotherapy

This may take place at appropriate facility within the sites. A dose of approximately $1x10^8$ cells/m^2 EBV-specific CTLs will be infused not earlier than 14 days and not later

than 28 days following completion of the last dose of chemotherapy. 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 described below (see Table 3).

For BSA calculation, the Mosteller formula will be used (refer to Appendix 4). Patients will be premedicated with Paracetamol or acetaminophen (or equivalent) and diphenhydramine or chlorpheniramine (or equivalent). EBV-specific CTLs will be given by IV injection through either a peripheral or a central line. The CTL infusion will be supervised by a delegated Investigator or trained Study Nurse and monitoring will be undertaken according to institutional standards for administration of blood products. The 2nd cycle of EBV specific-CTLs will be given 14 days after the 1st cycle.

Immunotherapy will be continued after 2 cycles to patients who show clinical benefit (CR, PR, SD) to initial immunotherapy, or in PD cases, if the clinician assesses that there may be benefit from further immunotherapy such as if they are asymptomatic with no organ threatening disease (refer Table 3).

The 3rd cycle of EBV-specific CTLs will not take place until the patient has been monitored for 6 weeks after the 2nd cycle of EBV-specific CTLs. EBV-specific CTL infusion (after the first 3 cycles of immunotherapy) will be administered at every 8 weeks intervals.

5.6.6 Immunotherapy Treatment Delay/ Modification/ Omission/ Termination

In view of variability of individual patient's T cells, EBV-specific CTL infusions may not be available in time or might not have enough vials available for the scheduled 6 infusions. In such cases, chemotherapy cycle(s) and/or EBV-specific CTL infusions may be adjusted after discussion between the Site PI, coordinating investigator and sponsor.

Patients who experience hypersensitivity during EBV-specific CTL infusion will have the infusion stopped and will have their blood pressure, pulse rate and oxygen saturation recorded at 5-minute intervals and IV hydrocortisone 100 mg will be administered. After 15 minutes, if the symptoms have completely resolved, the EBV-specific CTL infusion will be recommenced at 25% the infusion rate. If patients continue to experience infusion related reactions, EBV-specific CTL infusion will be abandoned and omitted for the cycle.

Patients who experience hypersensitivity reactions for 2 or more cycles or have to omit 2 consecutive cycles of immunotherapy due to Grade 3 and above AEs, will be discontinued from further EBV-specific CTL therapy. These patients will be followed up on survival status and initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment.

Further details on management of AEs related to EBV-specific CTL therapy can be found in Appendix 3.

Table 3: Treatment Schedule of Patient on Arm A

Week	-4	0	4	8	12	16	20	0	2	8	16	24	32
Stage	0 (Pre-Treatment) Preparation of Immune Cells	1						2 (only for CR, PR, SD, or asymptomatic PD and then decided by the clinician)					
Chemotherapy Cycle	0	1	2	3	4	5*	6*						
**EBV-specific CTL Infusion Cycle								1	2	3	4	5	6

*Additional chemotherapy cycle(s) (i.e. 5th and or 6th chemo in Arm A patient) might be given upon discretion of Investigator, if EBV-specific CTL infusions are not available in time for the 1st scheduled infusion. The EOC4 scan will be noted when EBV-specific CTLs are available at the end of chemotherapy cycle 4 and EOC6 scan will be noted when Arm A patient receives 6 cycles of chemotherapy. ** 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.

5.6.7 Chemotherapy – Patients on Arm B

Pre-medication will be administered accordingly; followed by gemcitabine 1000 mg/m^2 and carboplatin AUC2 will be administered on a Day 1, 8 and 15 schedule every 4 weeks. Patients will receive a total of 6 cycles of chemotherapy. The pre-medication and chemotherapy administration, modification, omission and termination will be as per Sections 5.6.3 and 5.6.4. For carboplatin dosage calculation, the Calvert's formula will be used. Note the GFR used in Calvert's formula to calculate AUC-based dosing should not exceed 125 mL/ min [49].

In the event of disease progression after 2 cycles of chemotherapy, the patient may proceed to alternative salvage treatment such as palliative radiotherapy as advised by the attending physician and exit the study treatment. These patients will then undergo procedures detailed under the EOT visit and also be followed-up on survival status and initiation of subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment.

6 SCHEDULE OF STUDY PROCEDURES

6.1 Study Method

Written informed consent will be obtained after the study has been fully explained to each subject prior to the conduct of any screening procedures or assessments. The screening period will start once the informed consent is signed.

6.1.1 Stage 0: Pre-treatment Phase

All pre-treatment screening procedures to be completed within 4 weeks of obtaining informed consent, prior to initiating 1st chemotherapy.

Prior to randomization

- Medical History, Medication History
- Demographics
- Physical Examination
- Vital Signs (blood pressure [BP], pulse rate, Weight, Height, ECOG PS)
- FBC and differential counts, serum chemistry (for Arm A patients, results must be within 7 days from date of venesection of peripheral blood for preparation of EBV-LCL and subsequent CTL generation)
- Urine pregnancy test
- HBsAg, HIV
- Electrocardiogram (ECG)
- CT or MRI, of relevant disease sites (within *4 weeks of C1D1*)

Prior to initiating 1st chemotherapy

- Randomization (prior to first dose of chemotherapy premedication and chemotherapy)
- Venesection of approximately 300 mL (up to 350mL) of peripheral blood for preparation of EBV-LCL and subsequent CTL generation – only if patients are randomized to Arm A
- HLA-typing – only if patients are randomized to Arm A
- Adverse Events (AE)s/ serious AEs (SAEs) review, concomitant medication/ therapy review

6.1.2 Arm A

6.1.2.1 Stage 1: Chemotherapy

- QoL assessment before 1st dose of chemotherapy
- Physical examination before each cycle of chemotherapy
- Vital signs [Blood Pressure (BP), pulse rate, weight, ECOG PS) before each cycle of chemotherapy
- Full Blood Count (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.
- Pre-medication before chemotherapy administration
- Chemotherapy administration as applicable on Day 1, Day 8 and Day 15 of each treatment cycle
- CT or MRI of relevant disease areas after completion of 2nd and 4th (and 6th if applicable) cycle of chemotherapy
- QoL assessment after completion of 2nd and 4th (and 6th if applicable) cycle of chemotherapy
- AEs/ SAEs review, concomitant medication/ therapy review and survival status follow-up at each scheduled visit
- Research bloods* (approximately up to 40 mL, as much as possible), within 3 days before commencement of cycle 1 chemotherapy, and after completion of every 2 cycles of chemotherapy, preferably on the day of completion of the chemotherapy cycle or the day after.
    - Immune function assays including analysis of EBV-specific CTL frequency using pentamer analysis, ELISPOT or CTL assays
    - Cytotoxicity assays to look at specificity of response will be done in patients on whom the appropriate reagents are available
    - PCR for EBV DNA
    - PBMC for T-cell isolation for FACS and extraction of RNA

    **At least 50 Arm A patients from sites in Singapore, Malaysia, Taipei and Taoyuan only, Sponsor will issue an official memo to sites to notify the omission of the study procedure research blood collection once sufficient samples of research blood have been collected. Sites who administer 1 to 2 additional cycles of chemotherapy (i.e. 5th GC chemotherapy cycle with or without 6th GC chemotherapy), the research blood collection will be done at end of completion of chemotherapy cycle.*

6.1.2.2 Stage 2: Immunotherapy

- Physical examination before each cycle of immunotherapy
- Vital signs (BP, pulse rate, weight, ECOG PS) before each cycle of immunotherapy
- FBC and Serum Chemistry within 3 days before the start of each immunotherapy cycle
- ECG will be performed before each cycle of immunotherapy
- CT or MRI will be performed approximately 7 weeks after 1st infusion of CTL and subsequently 7 weeks after each cycle of immunotherapy, before the next cycle of immunotherapy

- QoL assessment after completion of 2nd dose of CTL infusion and before 3rd dose; and after completion of 4th dose of CTL infusion and before 5th dose
- AEs/ SAEs review, concomitant medication/ therapy review and survival status follow-up at each scheduled visit
- Research bloods* (up to approximately 40 mL, or as much as possible), within 3 days before each cycle of immunotherapy
  - Immune function assays including analysis of EBV-specific CTL frequency using tetramer analysis, ELISPOT or CTL assays
  - Cytotoxicity assays to look at specificity of response will be done in patients on whom the appropriate reagents are available
  - PCR for EBV DNA
  - PBMC for T cell isolation for FACS and extraction of RNA

  **At least 50 Arm A patients from sites in Singapore and Malaysia, Taipei and Taoyuan only. Sponsor will issue an official memo to sites to notify the omission of the study procedure research blood collection once sufficient samples of research blood have been collected.*

6.1.2.3 End of Treatment

End of Treatment Visit evaluation is to be performed approximately 30 days (+/- 5 days), after the completion of the last chemotherapy or immunotherapy infusion.

- ECG
- Physical examination
- Vital signs (BP, pulse rate, weight, ECOG PS)
- FBC, differential counts and serum chemistry
- CT or MRI of relevant disease areas
- QoL assessment
- AEs/ SAEs review, concomitant medication/ therapy review and survival status

6.1.3 Arm B

6.1.3.1 Chemotherapy

- QoL assessment before 1st dose of chemotherapy
- Physical examination
- Vital signs (BP, pulse rate, weight, ECOG PS)
- 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.
- Pre-medication before chemotherapy administration
- Chemotherapy administration as applicable on Day 1, Day 8 and Day 15 of each treatment cycle
- CT or MRI of relevant disease areas after completion of each even cycle of chemotherapy
- QoL assessment after completion of 2nd cycle, 4th cycle and 6th cycle
- AEs/ SAEs review, concomitant medication/ therapy review and survival status follow-up at each scheduled visit
- Research bloods* (approximately up to 40 mL, as much as possible), within 3 days before commencement of cycle 1 chemotherapy, after completion of every 2 cycles of chemotherapy and after completion of cycle 5 chemotherapy, on the day of completion of the chemo cycle or the day after.
    - Immune function assays including analysis of EBV-specific CTL frequency using pentamer analysis, ELISPOT or CTL assays
    - Cytotoxicity assays to look at specificity of response will be done in patients on whom the appropriate reagents are available
    - PCR for EBV DNA
    - PBMC for T cell isolation for FACS and extraction of RNA

    **At least 10 Arm B patients from sites in Taipei and Taoyuan only. Sponsor will issue an official memo to sites to notify the omission of the study procedure research blood collection once sufficient samples of research blood have been collected.*

6.1.3.2 End of Treatment

End of Treatment Visit evaluation is to be performed approximately 30 days (+/- 5 days), after the completion of the last chemotherapy or immunotherapy infusion.

- Physical examination
- Vital signs (BP, pulse rate, weight, ECOG PS)
- FBC, differential counts and serum chemistry
- CT or MRI of relevant disease areas
- QoL assessment
- AEs/ SAEs review, concomitant medication/ therapy review and survival status

6.1.4 Follow-up Schedule for Surviving Patients

Following EOT, patients will be followed up for survival status via phone call every 12 weeks (+/- 5 days).

Patients who progressed and commenced salvage therapy will be followed up for their survival status via phone call. Subsequent antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study treatment should be recorded.

6.2 Endpoints Response Assessment and Definition

6.2.1 Overall Survival (Primary Objective)

OS is defined as the interval from the day of randomization until death from any cause. Date of death will be based on death certificates (if available) or confirmation with care-givers/ next-of-kin, to the extent possible.

Survivors and lost to follow-up patients are censored at the date of last follow-up.

Survival follow-up will be done every12 weeks from EOT(phone call follow-up). To minimize loss to follow-up, site must make at least 3 attempts to contact subject and at least 3 attempts to contact their next-of-kin/ caregiver. All efforts to contact the subjects will be documented in the source documents. For countries that allow sites to search the death registries, annual search will be performed by site to check on the lost to follow-up patients. Searches across social media and newspapers (obituary section), where available, will also be conducted to the greatest extent possible.

6.2.2 Progression Free Survival (Secondary Objective)

PFS is defined as the interval from the day of randomization until disease progression or death from any cause. Patients who receive subsequent anti-cancer therapy will be censored at the date of last tumor assessment prior to first subsequent therapy date. Patients free from disease progression who are alive or lost to follow-up are censored at the date of last scheduled tumor assessment. Disease progression will be evaluated via imaging.

6.2.3 Overall Response Rate and Clinical Benefit Rate (Secondary Objective)

Tumor assessment will be according to RECIST 1.1 criteria. All patients who receive any infusion will be evaluable for response. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

At baseline, tumor lesions/ lymph nodes will be categorized measurable or non-measurable as follows:

Measurable tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.
- For malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

The investigator will identify up to 5 measurable lesions (and a maximum of two lesions per organ) to be followed for response. Serial measurements are to be done with CT or MRI. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10mm.
- PR: At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
- PD: At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more unequivocal new lesions is also considered progression.
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

ORR is defined as the proportion of individuals who achieve a BOR of CR or PR while on treatment, taking as reference the tumor measurement at baseline. Hence the ORR will include the combined response to chemotherapy and to CTL therapy for Arm A. This will include late responses as is characteristic of immunotherapy. For Arm B, the ORR will include the response to chemotherapy only.

CBR is defined as the proportion of individuals who achieve CR, PR or SD while on treatment, taking as reference the tumor measurement at baseline. Hence, the CBR will include the best clinical benefit achieved to chemotherapy and to CTL therapy for Arm A. This will include late responses as is characteristic of immunotherapy. For Arm B, the CBR will include the response to chemotherapy only.

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

6.2.4 Quality of Life (QoL) (Secondary Objective)

QoL will be assessed by means of validated questionnaires completed by patients. The EORTC QLQ-C30 [1] will be used. 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, based on the recommended EORTC procedures [2]. The questionnaire will be available in local languages. QoL assessment is to be performed at the following timepoints.

Arm A

- Before 1st dose of chemotherapy
- After completion of 2nd cycle, 4th cycle and 6th cycle (where additional cycles of chemotherapy are applicable) of chemotherapy
- After completion of 2nd dose of CTL infusion and before 3rd dose
- After completion of 4th dose of CTL infusion and before 5th dose
- During EOT

Arm B

- Before 1st dose of chemotherapy
- After completion of 2nd cycle, 4th cycle and 6th cycle of chemotherapy
- During EOT

6.3 Safety Assessment

Safety assessments will consist of physical examinations, monitoring and recording all AEs and SAEs, monitoring selected laboratory values, and periodic measurement of vital signs and ECGs.

The following sections describe the methods and timing for assessing and recording, safety parameters, as well as the procedures for eliciting, recording, and reporting AEs and intercurrent illnesses and the type and duration of follow-up of subjects with AEs.

6.3.1 Definitions

An AE is defined as any untoward medical occurrence in a subject enrolled in the clinical trial, and it does not necessarily have to have a causal relationship with the study treatment. The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, or disease temporally associated with the use of a medicinal product observed, whether or not considered related to the medicinal product.

- Any new disease or exacerbation of an existing disease. Worsening of primary disease is not defined as an AE.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test [e.g. electrocardiogram (ECG)] that results in symptoms, a change in treatment, or discontinuation from medicinal product.
- Reoccurrence of an intermittent medical condition (e.g. headache) not present at baseline.

An abnormal laboratory test result may be considered as an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not. A laboratory result should be considered to be an AE if it:

- Results in the withdrawal of study treatment
- Results in the initiation of medical intervention
- Results in any out-of-range laboratory value that, in the investigator's or sub-investigator's judgment, fulfills the definitions of an AE with regards to the subject's medical profile
- Increases in severity compared to baseline by ≥ 2 NCI-CTCAE, version 4.0

It is the responsibility of the investigator and sub-investigator to review the results of all laboratory tests as they become available. This review is to be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if it is an abnormal (i.e. clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. If an abnormal laboratory value is determined by the investigator to be a clinically significant change from baseline for the individual subject, the abnormal value is considered an AE.

A TEAE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered to have a causal relationship with the medicinal product.

All medical conditions and abnormalities present during subject evaluation at screening and up until the initiation of the study treatment should be documented on the Medical History or the Physical Evaluation Electronic Case Report Form. Recording of AEs should commence from the time of informed consent in order to ensure subject safety. Worsening of these conditions and new symptoms, physical signs, syndromes, or diseases should be considered as AEs, except when related to the primary disease.

All AEs will be followed up until resolution or when the subject exits the trial.

A SAE is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening, ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (not an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of hospitalization (however, hospitalization for the purposes of this clinical trial or for examination for disease or for treatment of PD will not be regarded as an SAE);
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Or is any other medically significant event that, based on appropriate medical judgment, might jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

For the purposes of this study, the following adverse events are not reported as SAEs:

- Hospitalizations related to disease progression
- Administration of chemotherapy or CTL immunotherapy; or
- Unrelated scheduled elective surgery; or
- Convenience purposes, e.g. transportation difficulties, timing of blood transfusion.

A non-serious AE is any AE that does not meet the criteria for an SAE.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the IP and is unexpected (i.e. not listed in the investigator brochure; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol. An event is causally related if there is a reasonable possibility that the intervention caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event.

An immediately reportable event (IRE) is any SAE, or any AE that necessitates discontinuation from the study treatment. Pregnancy is also defined as an IRE (although normal pregnancy is not an AE, it requires discontinuation from the study treatment). These events must be reported to the sponsor according to procedures specified in Sections 6.3.4.1 and 6.3.5.

Severity: AEs will be graded according to the NCI-CTCAE version 4.0 and reported as indicated in the eCRF. For AEs that are not described or covered by the NCI-CTCAE version 4.0, severity will be graded as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.3.2 Attribution of the AE:

Causal relationship with study treatment: AEs should be judged as related or unrelated to study treatment as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

6.3.3 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs and record AE information offered spontaneously by subjects. To avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded in the source documents and the eCRF.

The sponsor must be notified immediately of any IREs according to the procedures specified in Section 6.3.4.1. Special attention should be paid to recording hospitalization status and concomitant medications used.

6.3.4 Immediately Reportable Events

6.3.4.1 IREs Reportable Within 24 Hours

To ensure patient safety, SAEs that are identified from time of informed consent to EOT must be reported to sponsor. Any new SAEs experienced after EOT should be reported to sponsor only if the investigator determines it to be reasonably associated with use of the investigational product.

Immediately after the investigator becomes aware of any SAE or confirmed pregnancy, the investigator must report the event to sponsor within 24 hours. The eCRF AE page must be completed and notified to sponsor within 24 hours.

Any subject experiencing an SAE should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

In accordance with applicable regulations and local laws, the investigator and the CRO will identify and report within the required timeframe to regulatory authorities, and to IRBs/IECs where required, all Adverse Drug Reactions (ADRs) that are determined to be both serious and unexpected.

6.3.5 Investigator Reporting: Notifying the Sponsor (Including SUSARs)

To report SAE/IRE, the AE page of the eCRF must be completed and submitted to sponsor/ designated pharmacovigilance within 24 hours. All applicable sections of the eCRF must be completed in order to provide a clinically thorough report. The investigator must assess the causality of each SAE to each specific study treatment. The initial completion of the AE eCRF will be considered an initial SAE/IRE report.

Within the following 48 hours, the investigator must provide further information on the SAE or the IRE in the form of a written narrative. This should include any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing SAEs/IREs should be provided promptly to pharmacovigilance.

6.3.6 Investigator Reporting: Notifying the IRB/IEC (Including SUSARs)

6.3.6.1 Reporting Process

SAE/IRE will be reported to the IRB/IEC as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB promptly. Copies of each report and documentation of IRB notification will be kept in the investigator's study file.

6.3.6.2 Other Reportable Events

The following events are also reportable to the IRB/IEC:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected AE that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome);

- Any AE that would cause the sponsor to modify the investigator's brochure, protocol or ICF, or would prompt other action by the IRB to assure protection of human patients;
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected;
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value;
- Change in safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Breach of confidentiality;
- Change to the protocol taken without prior IRB/IEC review to eliminate apparent immediate hazard to a research participant;
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team;
- Protocol violation (meaning an accidental or unintentional deviation from the IRB/IEC approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of patients.

6.3.7 Sponsor Reporting: Notifying the Regulatory Authority (Including SUSARs)

If the AE is serious, related and unexpected, sponsor and designated CRO will report the event in an expedited fashion [i.e. Investigational New Drug (IND) Safety Report] to the regulatory authorities of participating countries in the study.

All unexpected fatal or life-threatening suspected AEs will be reported to the regulatory authority no later than 7 calendar days after the sponsor's initial receipt of the information. Any relevant additional information that the sponsor obtains that pertains to submitted safety report must be submitted as a follow-up report without delay, as soon as the information is available, but no later than 15 calendar days after the sponsor receives the information.

Any other SAE observed during conduct of the study, regardless of whether the event is considered drug related, as soon as possible but in no case later than 15 calendar days after sponsor becoming aware of its occurrence.

6.3.8 Sponsor Reporting: Notifying Participating Investigators (Including SUSARs)

It is the responsibility of sponsor and designated CRO to notify all participating investigators, in a written safety report, of any AE associated with the use of the drug

that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human patients.

6.3.8.1 IREs Reportable Within 3 Working Days

A non-serious event (including abnormal laboratory finding) that requires discontinuation of the chemotherapy or investigational product should be reported to sponsor within 3 working days. The eCRF AE page must be completed and notified to sponsor accordingly.

Any Grade 2 and above autoimmune reactions should be reported to sponsor within 3 working days. The eCRF AE page must be completed and notified to sponsor accordingly.

6.3.8.2 Pregnancy

The investigator or sub-investigator will instruct female subjects who are women of child-bearing potential (WOCBP) and male subjects whose partners are WOCBP to use an effective method of contraception until completion of the last study treatment. The investigator or sub-investigator will confirm the presence or absence of pregnancy and record the result in the source documents. Unless the subject or his/her partner(s) are sterile (i.e. a woman who has had an oophorectomy and/or hysterectomy or who has been postmenopausal for at least 12 consecutive months or a man who has had an orchidectomy) or remain abstinent, an acceptable method of contraception must be used. Acceptable contraceptive methods include vasectomy, tubal ligation, vaginal diaphragm, hormonal contraceptives, intrauterine device (IUD), birth control implant, condom and contraceptive sponge with spermicide.

Before enrolling WOCBP or male subjects whose partners are WOCBP in this clinical trial, the investigator or sub-investigator must explain the following:

- General information
- The information in the Informed Consent Form (ICF)
- Pregnancy prevention information
- Investigational product interactions with hormonal contraceptives
- Contraceptives in current use

The investigator or sub-investigator will advise WOCBP and male subjects whose partners are WOCBP of the importance of avoiding pregnancy during trial participation and the potential risk factors involved in an unintentional pregnancy. The subject must read the explanatory information and sign the ICF based on a thorough understanding of those risk factors.

During the trial, WOCBP and male subjects whose partners are WOCBP should be instructed to contact the investigator or sub-investigator immediately if they suspect that pregnancy has occurred (e.g. missed or late menstrual cycle).

If pregnancy is suspected while the female subject is receiving treatment, investigational product or chemotherapy administration must be immediately stopped (taking into consideration any potential withdrawal risks) and withheld until the result of a pregnancy test is known. If pregnancy is confirmed, the female subject must be withdrawn from the study treatment, undergo EOT visit and followed up on survival status. For Male subjects whereby their partner/spouse become pregnant, they will continue with the study treatment. The investigator or sub-investigator must notify the sponsor (refer to the contact information in the cover pages) within 24 hours of any pregnancy occurring in a female subject or a female partner of a male subject during investigational product or chemotherapy exposure and follow the reporting procedures specified for this study.

The examinations specified to be conducted at early termination must be performed for the subject unless the examination might affect the pregnancy (e.g. x-ray).

A separate consent to follow-up on the progress of the pregnancy will be obtained for the female subject and the partner/spouse of the Male subject. Upon obtaining consent, the sponsor will then follow-up on the outcome of the pregnancy. Pregnancy will only be included in the AE column of the eCRF if there is an abnormality or complication reported.

In addition, the investigator or sub-investigator must perform appropriate follow-up for up to 6 to 8 weeks after birth and report to the sponsor.

6.3.9 Follow-up of Adverse Events

6.3.9.1 Follow-up of Non-Serious Adverse Events

Non-serious AEs that are identified from time of informed consent to EOT visit must be recorded on the AE page of the eCRF, with the current status noted. All non-serious events that are ongoing at that time will be recorded as "ongoing" in the eCRF.

6.3.9.2 Follow-up of Post-Treatment Serious Adverse Events

SAEs that are identified from time of informed consent to EOT visit must be recorded on the AE page of the eCRF and reported to sponsor according to the procedures specified. This includes both unresolved previously reported SAEs and new SAEs. The investigator should follow these SAEs until the event is resolved or the subject has exited the trial. Resolution means the subject has returned to baseline status or the investigator does not expect any further product involvement or worsening of the subject's condition. The investigator should continue to record any treatment (medication, therapy, etc.) in the eCRF and report any significant follow-up information to sponsor up until the time the event is resolved.

Patients who commence salvage therapy will exit the study treatment. These patients will be followed up on survival status only.

6.4 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will review the progress of the study and perform annual reviews of the safety data and provide recommendations to the sponsor whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The IDMC may also provide recommendations as needed regarding study design. The IDMC will convene at least once a year. The IDMC's specific activities will be defined by a mutually agreed upon charter, which will define the IDMC's membership, conduct and meeting schedule.

While the IDMC will be asked to advise sponsor regarding future conduct of the study, the sponsor retains final decision-making authority on all aspects of the study.

6.5 Discontinuation Criteria and Procedures

6.5.1 Entire Trial

The sponsor should be notified promptly if the trial is terminated at a given site. If the sponsor decides to terminate or suspend the trial for safety or other unanticipated reasons, the sponsor will promptly notify the investigators, IRBs/ IECs, and regulatory authorities as required by the applicable regulatory requirements.

6.5.2 Individual Trial Subject

If an individual subject is withdrawn from the trial, the reason given must be fully evaluated and recorded appropriately in the source documents and the eCRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal.

All subjects have the right to withdraw from the trial at any time without prejudice. If a subject chooses to withdraw from the study treatment, he or she will undergo EOT and be followed up on survival status and further data collection subsequent to the withdrawal from the interventional portion of the study provided that the subject consents to it.

If a subject withdraws from the trial and does not consent to continued follow-up of associated clinical outcome information, an investigator may review study data related to the subject collected prior to the patient's withdrawal from the study. Also, an investigator may review public records such as survival status. There is no data collected from the subject from the time of withdrawal.

Sponsor should be notified promptly when a subject is withdrawn from study treatment or trial. Withdrawn or discontinued subjects after initiation of treatment will not be replaced.

The investigator can discontinue a subject's participation in the trial at any time if medically necessary.

In addition, a subject to whom any of the following criteria apply must be withdrawn from the study treatment:

a) Occurrence of any AE, intercurrent illness, or abnormality in clinical laboratory test results which, in the opinion of the investigator, warrants the subject's withdrawal from the study treatment.

b) For Arm A subjects: Reasons [unrelated to the Good Manufacturing Practice (GMP) processes] which may result in no/ insufficient CTLs generated, for e.g. the inability to generate sufficient LCLs despite multiple attempts and/or slow T cell expansion rate that are more akin to intrinsic factors.

c) Arm A subject who experiences hypersensitivity reactions for 2 or more cycles.

d) Suspension of chemotherapy for more than 28 days or 2 consecutive cycles of immunotherapy.

e) Irreversible or life-threatening toxicity.

f) Rapid clinical or radiological progression of disease.

g) Grade 3 or 4 toxicity considered to be primarily related to CTL injection.

h) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.

i) Female subject becomes pregnant.

A subject to whom any of the following criteria apply must be withdrawn from the trial:

a) Subject is lost to follow-up.

b) Withdrawal of consent.

6.5.3 Screen Failure

A screen failure is a subject from whom informed consent is obtained and documented in writing (i.e. subject signs an ICF), but who is subsequently considered ineligible prior to the start of chemotherapy (Stage 1). Screen failure subjects may be re-screened at any time if the condition limiting their participation is no longer applicable, but they will be assigned a new screening number.

6.5.4 Definition of Treatment Completion and Study Completion

For the purposes of this study, subjects will be defined as having completed treatment if they fulfil any of the following criterions:

- Completion of treatment as defined in the study design
    - For patients in Arm A, completion of at least 4 cycles of chemotherapy (Stage 1), followed by 6 cycles of EBV-specific CTL infusions (Stage 2).

- For patients in Arm B, completion of 6 cycles of chemotherapy.

Study completion is defined as completing all study required follow-ups (including survival follow-up) at end of the trial. Death, Lost to Follow-up, Withdrawal of consent to further contact will be deemed as non-completion.

6.5.5 Definition of Subjects Lost to Follow-up

To minimize lost to follow-up, site must make at least 3 attempts to contact subject and at least 3 attempts to contact their next-of-kin/caregiver over a total period of 6 months (from the date of first attempt). All efforts to contact the subjects will be documented in the source documents. For subjects who cannot be contacted at or before the time of the scheduled final visit and who do not have a known reason for discontinuation (e.g. withdrawn consent or AE), the reason for discontinuation will be indicated as "lost to follow-up".

6.5.6 Protocol Deviation

This trial is intended to be conducted as specified in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or error (e.g. violation of informed consent process, or subject enrolled in violation of eligibility criteria), the investigator (or a designee) must contact the sponsor by telephone at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor and reviewed by the medical monitor.

7 RESTRICTIONS

7.1 Prohibited Medication

The below listed therapies will be prohibited from the time of the subject signed informed consent until completion or discontinuation from the study.

- Chemotherapy (other than gemcitabine and carboplatin) or any other therapies for treatment of NPC
- Other interventional investigational therapies

Gemcitabine is a potent radiosensitizer [47] and local radiotherapy is prohibited during chemotherapy phase for treatment of NPC. However, local radiotherapy or radiofrequency ablation is not contraindicated during CTL immunotherapy phase and will be based on Investigator discretion.

7.2 Other Restrictions

7.2.1 Contraception

Unless the subject or his/her partner(s) are sterile (i.e. a woman who has had an oophorectomy and/or hysterectomy or who has been postmenopausal for at least 12 consecutive months or a man who has had an orchidectomy) or remain abstinent, an acceptable method of contraception must be used. Acceptable contraceptive methods include vasectomy, tubal ligation, vaginal diaphragm, hormonal contraceptives, IUD, birth control investigational implant, condom, and contraceptive sponge with spermicide.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size

Oncology trials with time-to-event primary endpoints are typically powered for the log-rank test to detect a given hazard ratio (HR) under the assumption of proportional hazards. When the assumption of proportional hazards holds, the survival curves are expected to start separating from the beginning of follow-up such that the true HR is constant and independent of the time period over which it is calculated. Although the log-rank test is still valid under the scenario of non-proportional hazards, the power of the test is reduced.

In this trial, a non-proportional hazards situation may prevail due to a minimum 4-6 months delay in separation of the survival curves following randomization for the following reasons:

1) As both arms receive identical treatment (chemotherapy) for the first 4 cycles, or potentially up to 6 cycles depending on the availability of CTL infusions after 4 cycles of chemotherapy, an approximate 6 months delay in separation of the survival curves is expected 'by design'.

2) A potential delay in therapeutic response to CTL treatment may further extend the time until the survival curves can be expected to separate.

Currently it is unknown whether there will be a delay in therapeutic response to CTL treatment. We can therefore expect the minimum delay in separation of the curves to fall in the range of 4-6 months.

A total of 330 patients will be enrolled and randomized in a 1:1 ratio to Arm A and Arm B. This number of events is sufficient to detect a 33% reduction in the risk of death in Arm A, as compared with Arm B (HR of 0.67) using a 2-sided log-rank test with 71% power and an overall significance level of 5%, assuming median survival of 18 months in the control arm and a 6 month delay in separation of the survival curves. Assuming survival times are exponentially distributed, this sample size and target number of

events allows a corresponding detection of 9 months difference in median OS between the two arms. An accrual period of 5.5 years, an additional 3 years of follow-up, and a dropout rate of 10% are factored into the sample size calculations.

Table 4 shows how study power varies with 4, 6, and 8-month delays in separation of the survival curves.

Table 4: Power to Detect HR of 0.67 Assuming Delays in Separation of Survival Curves of 4, 6 & 8 Months

Number of Patients	Number of Events	Power* (true HR post-separation of survival curves = 0.67)		
		4-month delay	6-month delay	8-month delay
330	280	80%	71%	63%

*Power for each design is calculated from 7000 simulated trials, assuming a true HR of 1 before separation of the curves and a true HR of 0.67 thereafter. HR, hazard ratio.

No interim analysis will be performed for this study.

The final analysis may be triggered when 280 events have been observed to conclude the OS result, or at the discretion of the Sponsor if it is not likely that 280 events will be reached in a reasonable timeframe, to summarize the OS findings which may not be conclusive.

8.2 Statistical Analysis

All statistical analyses will be performed using Statistical Analysis System (SAS). Details on statistical analyses will be described in the Statistical Analysis Plan (SAP).

8.2.1 OS and PFS

Differences between treatment groups for OS and PFS will be tested using a stratified log-rank test, accounting for the two stratification factors of country and disease stage. Corresponding Hazard Ratios with 95% CI will be estimated using stratified Cox proportional hazards regression. The Kaplan-Meier (KM) method will be used to plot OS and PFS by treatment group. Comparisons of 2,3 and 5-year OS will also be made using the KM plots. The assumption of proportional hazards will be assessed, and if violated, other measures to estimate treatment benefit will also be reported. Where small cell counts (< 10 subjects) are observed in any of the stratum, an assessment will be made regarding whether strata can be meaningfully pooled or the stratification factor removed. The details of these statistical analysis approaches will be included in the SAP, prior to the final analysis.

8.2.2 2, 3 and 5-year OS

2, 3 and 5-year OS rates for each arm will be estimated from the KM plot.

8.2.3 ORR and CBR

The overall response rate and clinical benefit rate will be estimated with 95% CI for each treatment arm separately. The response rates between the two arms will be compared using logistic regression with the stratification factors included in the model.

8.2.4 QoL

Maximum likelihood estimation with all available repeated measurement data will be used to estimate the mean and standard error of QoL values at each time point for each arm [42]. As the two arms have different treatment schedules, we have tried to keep timepoints for QoL assessments in sync for patients on either arm, in order to compare QoL values. All mean QoL value with 95% CI at each time point and treatment arm will be plotted together and examined graphically.

8.2.5 Biomarker Analyses

8.2.5.1 Exploratory Analyses Using Adaptive Signature Design

As biomarkers predicting the effect of EBV-specific CTL therapy on OS have not been elucidated, development and validation of a predictive biomarker signature will follow that of the Cross-Validated Adaptive Signature Design (CVASD) [50], where the discovery and evaluation for a potential biomarker signature will be performed during the final analysis at end of study. The CVASD approach will allow for more efficient use of the limited data stemming from partial ascertainment of research bloods.

As this is an exploratory analysis, the overall type I error rate will not be partitioned as it would be in the confirmatory setting, where one part is utilized for the subset analysis (involving marker-positive subjects identified by the classifier) and the other for the comparison at the overall (All-comers) level. Instead, the conventional $p \leq 0.05$ threshold of statistical significance will be used to test for a difference between treatments in subjects classified as biomarker-positive.

A candidate list of biomarkers will be pre-specified based on their clinical rationale, and data obtained from prior research (refer to the SAP for this candidate list). Research bloods obtained at baseline (prior to initiation of chemotherapy) and during the 4 cycles of chemotherapy prior to initiation of EBV-specific CTL will be analyzed and values of each candidate biomarker determined. It is hypothesized that baseline biomarker values as well as the change from baseline during 4 cycles of chemotherapy prior to initiation of EBV-specific CTL could be predictive of the effect of EBV-specific CTL therapy on OS. Given the lower ascertainment of post-baseline biomarker samples, two candidate lists will be used for the CVASD analysis: (1) comprising only biomarkers collected at baseline (prior to initiation of chemotherapy) and (2) comprising of both biomarkers collected at baseline as well as those collected during the 4 cycles of chemotherapy prior to initiation of EBV-specific CTL therapy.

A K-fold cross-validation procedure based on subjects with baseline research blood will be implemented to both develop and then validate the classifier of biomarker signature positive subjects. The details of this procedure are outlined in the SAP.

8.2.5.2 Other Exploratory Analyses

Additional 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 will 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 only be regarded as exploratory.

8.2.6 Analysis Sets

The following three analysis populations will be evaluated for this study:

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 analyzed 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).

The **modified intent-to-treat (MITT)** analysis population is defined as all randomized subjects who are on the trial for at least 5 months (150 days) post-randomization. The MITT analysis population will be used for supportive analyses of the primary and secondary endpoints.

The **Per protocol (PP)** analysis population is defined as subjects who meet the ITT criteria and are not associated with major protocol violations.

Subjects will be analyzed in the treatment group corresponding to the actual treatment received.

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. Additionally, for Arm A, safety will also be summarized separately for the periods before and after receipt of the first CTL infusion.

8.3 Interim Analysis

No Interim Analysis (IA) will be conducted for this trial.

8.4 Handling of Missing Data and Sensitivity Analysis

All necessary effort will be made to avoid missing data. However, in the event there is missing data appropriate methods will be used to adjust for the missing data and sensitivity analyses will be conducted to demonstrate the robustness of the study conclusions. The details of methods for handling of missing data and sensitivity analyses will be included in the SAP.

9 MANAGEMENT OF INVESTIGATIONAL PRODUCT

The investigator, sub-investigator, study coordinator/nurse and/or designated representative will be responsible for the tracking and accountability of the investigational product.

Under no circumstances will the investigator and sub-investigator allow the investigational product to be used other than as directed by this protocol.

Detailed instructions on the tracking, accountability and management of the investigational product, from the initiation of blood sampling for establishment of the CTL, to the processing procedures, storage, dispensing and administration of the investigational product will be provided to the sites in a separate document.

Sites will be required to maintain an accurate and timely record of the investigational product, including, but not limited to:

- Tracking logs of blood samples from patients

- Processing logs of blood samples for establishment of the CTLs
- Handling of CTLs inventory and accountability logs
- Shipment and tracking logs to/from GMP facility
- Dispensing and administration logs of CTLs

10 RECORD MANAGEMENT

10.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons defined in the ICF as follows:

- The clinical trial team and authorized personnel
- The trial sponsor and its designated representatives
- The trial site's IRB/IEC
- The regulatory authority and other government agencies involved in ensuring the safety of clinical trial subjects

Direct inspection includes the authority to examine, analyze, verify, and reproduce any records and reports that are considered important to the evaluation of a clinical study.

10.2 Data Collection

1) Patient data from this trial will be collected using electronic CRF (eCRF), and/or other traceable and verifiable means.
2) An eCRF will be created for all screened subjects in the trial.
3) The investigator, sub investigator, or an authorized designee will create the eCRF according to the Electronic Data Capture (EDC) Operation manual or relevant documents provided by the sponsor.
4) After data is entered into the eCRF from the trial site, the investigator or sub investigator or authorized designee will be contacted by the sponsor or the sponsor's representative as necessary via the EDC system. The investigator, sub investigator or authorized designee will correct data as necessary.
5) After completion of all eCRF data cleaning and confirmation that all eCRF data are correct and complete, the investigator will attach an electronic signature. Thereafter, the data will be stored on CD-ROM or DVD-ROM and kept at the trial site.

6) Relevant paper records (ECG charts, SAE reports, etc) generated in the trial may also be collected by the sponsor after subject's identity are being blinded (if necessary, for adverse events reporting), and some of the information contained in these records will also be recorded in the eCRF.

7) Analysis results for the research bloods will be sent to the sponsor, separate from the EDC system.

10.3 File Management at the Trial Site

It is the responsibility of the investigator to ensure that the trial site files are maintained in accordance with Section 8 of the ICH GCP Guideline and as required by applicable local regulations. The investigator and trial site staff should take measures to prevent accidental or premature destruction of these documents.

10.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longer of the following 2 periods:

- A period of at least 15 years from the date of approval to manufacture the product is obtained (if development of the investigational product is discontinued, the date when development is discontinued)
- A period of at least 15 years from the date the trial is completed or terminated

The investigator must not dispose of any records relevant to this trial without either: (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (e.g. relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe and notice of the transfer will be submitted to the sponsor in writing.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial carefully in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations and maintain current direct knowledge of the progress of the trial, the sponsor (or representing CRO) monitors and will visit the trial site during the trial, in addition to maintaining frequent telephone and written communication.

11.2 Auditing

The sponsor (or representing CRO) may conduct audits at the trial site. Audits will include, but are not limited to, investigational product processing and tracking logs, presence of required documents, the informed consent process, and comparison of the eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may inspect the trial site during or after the trial. The investigator should contact the sponsor immediately if such an inspection occurs and must fully cooperate with inspections conducted at a reasonable time and in a reasonable manner.

12 ETHICS AND RESPONSIBILITY

This trial must be conducted in compliance with the protocol, the ICH GCP Guideline, and applicable local laws and regulatory requirements.

13 CONFIDENTIALITY

All information generated in this trial must be considered highly confidential and must not be disclosed to any persons not directly concerned with the trial without prior written permission from the sponsor. All subject confidentiality requirements of the region where the trial is conducted must be met. Subjects will be identified in the eCRF only by initials and subject screening ID number. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy all trial records.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the sponsor and the investigator.

14 FINANCIAL AND INSURANCE

14.1 Financing

Prior to initiation of the study, the principal investigator and trial site will conclude a clinical trial agreement with the sponsor. This agreement will specify the financial details agreed upon between the parties.

14.2 Insurance

The sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. Insurance shall be addressed in a separate agreement according to terms agreed upon between the principal investigator, trial site and the sponsor.

15 PUBLICATION POLICY

No data acquired in the conduct of this clinical trial may be published without prior mutual written agreement between the sponsor and the person(s) intending to publish the data. Procedures for publication will be determined by the sponsor after completion of the trial. The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between the sponsor and each investigator.

16 AMENDMENT POLICY

The investigator will not make any changes to this protocol without prior written consent from the sponsor and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it will be an overall change or a change for a specific trial site, must be handled as a protocol amendment. Any amendment to the protocol that appears indicated, as the trial progresses, will be fully discussed by the investigators and the sponsor. If agreement is reached regarding the need for an amendment, the amendment will be written by the sponsor. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility. Except for "administrative" or "non-substantial" amendments, investigators must await IRB/IEC approval of the protocol amendment before implementing any changes. Administrative amendments are defined as changes having no effect on the safety of the research subjects, scope of the investigation, conduct or management of the trial, quality or scientific value of the trial, or quality or safety of the investigational product used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately and the IRB/IEC notified within 5 working days. The sponsor will ensure protocol amendments are submitted to the applicable regulatory agencies.

When, in the judgment of the chairman of the IRB/IEC, the investigator, or the sponsor, an amendment to the protocol substantially alters the trial design or increases the potential risk to the subjects, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from each subject enrolled in the trial for continued participation.

17 APPENDICES

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, pulse rate)	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 (Stage 2)						End of Treatment (EOT)	Follow-up ^
	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, pulse rate)	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	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 (± 5 days), 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 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.*

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 within 4 weeks of screening.*

b *Additional blood (approximately 200mL, up to 250ml) 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 $\geqslant$ 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 and 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 cell (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 (i.e. up to a total of 6 cycles) if the autologous EBV-specific CTLs are not ready after EOC4 for infusion.*

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, pulse rate)	X	X [b]				X	
Height	X						
Weight	X	X [b]				X	
ECOG Performance Status	X	X [b]				X	
Urine Pregnancy Test	X						
FBC [+]	X [i]	X [j]	X [j]	X [j]		X	
Serum chemistry [h]	X [i]	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]		
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 [l]	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 signed consent 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 and, 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 12 months before4 weeks of screening or at screening

n To be conducted after completion of chemotherapy cycle 2, cycle 4, cycle 5 and cycle 6.

Appendix 3 Management of Adverse Events to the Immunotherapy (CTL Therapy)

The following will apply to adverse reactions occurring early < 24 hours post immunotherapy or late > 24 hours after Immunotherapy.

Early Reactions (< 24 hours post immunotherapy)

Early reactions are usually related to the cryopreserved components.

Common complications from Immunotherapy include mild increase in blood pressure not requiring intervention, and mild headache. Side effects from cryopreserved components may include mild flushing, slight slowing of the heart rate, and a "bad taste" in the mouth. Severe immediate reactions are rare after Immunotherapy and include acute pulmonary edema and dyspnea, persistent nausea and vomiting, increase in blood pressure that does not respond to medication with standard doses of furosemide and/or nifedipine, fever, anaphylactic shock, bradycardia and/or cardiac arrest.

Most common early reactions do not required intervention. In the event of a severe reaction, the patient should be immediately transferred to the ICU for intensive monitoring and intervention, which usually include BP support, steroids, and management of anaphylaxis.

Late Reactions (> 24 hours after immunotherapy)

Late reactions to immunotherapy may be related to a T-cell engraftment syndrome, tumor lysis syndrome, and rarely contamination of the product.

Symptoms and signs of late complications from immunotherapy include:

1) Systemic: Fever, skin rash mimicking acute GVHD, general feeling of unwellness
2) Cardio respiratory: Blood pressure changes (either hyper or hypotension), acute pulmonary edema and dyspnea, hypoxia, pulmonary infiltrates, capillary leak syndrome
3) Renal: Weight gain, renal impairment, hyperuricemia

The development of a severe late reaction necessitates immediate notification of the study Principal Investigator and transfer to the hospital for an urgent medical assessment. It is important to evaluate the patient and initiate therapy as quickly as possible since rapid deterioration is possible.

The immediate assessment and treatment may include:

- Intensive monitoring [BP, cardiovascular monitoring, pulse oximetry +/- Arterial Blood Gas (ABG)]
- CT of chest
- Steroids (single dose)
- Microbiological studies (especially blood cultures) and initiation of broad-spectrum antibiotics

- Blood pressure/Cardiovascular support: Early institution of inotropic medications. Limit fluid restriction to 20ml/kg is advisable.
- Fluid management/Renal support: Aggressive diuresis. Institute early involvement of the renal service for fluid management especially if evidence of capillary leak syndrome.
- Respiratory support: O_2 therapy should be initiated for all hypoxemic patients. Patients also may require intubation and mechanical ventilation.
- Management of tumor lysis syndrome if laboratory evidence.

Treatment of the engraftment syndrome may include scheduled methylprednisolone 0.5 mg/kg IV every 6-12 hours.

Appendix 4 Final Infusion Dosage Based On BSA

The **final infusion dosage** (i.e. number of cells to be infused) will be calculated by the Central Production Facility as follows:

Infusion Dosage (Based on BSA)

= Subject's BSA (calculated using Mostellar Formula) × Infusion Dose

$$= \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}} \times 1 \times 10^8 cells/m^2$$

= Number of cells (based on BSA), rounded up to the nearest 1 decimal place

Number of Vials to be Infused

$$= \frac{Number\ of\ cells\ (based\ on\ BSA)}{0.2 \times 10^8\ cells/vial}, \textit{rounded up to the nearest whole number}$$

Final Infusion Dosage (Based on Number of Vials to be Infused)

= Number of vials to be infused × (0.2×10^8 cells/vial)

BSA (Mostellar Formula)	$\sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$
Infusion Dose	$1 \times 10^8 cells/m^2$

Example 1:

Infusion Dosage (Based on BSA)

= 1.9001×10^8cells = 2.0×10^8cells, rounded up to the nearest 1 decimal place

Number of Vials to be Infused

$$= \frac{2.0 \times 10^8 \text{cells}}{0.2 \times 10^8\ cells/vial} = 10 \text{ vials}$$

Final Infusion Dosage (Based on Number of Vials to be Infused)

$= 10\ vials \times 0.2 \times 10^8\ cells/vial = 2.0 \times 10^8\ cells$

Example 2:

Infusion Dosage (Based on BSA)

= 2.01×10^8cells = 2.1×10^8cells, rounded up to the nearest 1 decimal place

Number of Vials to be Infused

$$= \frac{2.1 \times 10^8 \text{cells}}{0.2 \times 10^8\ cells/vial} = 10.5 \text{ vials} = 11 \text{ vials}, \textit{rounded up to the nearest whole number}$$

Final Infusion Dosage (Based on Number of Vials to be Infused)

$= 11\ vials \times 0.2 \times 10^8\ cells/vial = 2.2 \times 10^8\ cells$

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