SPONSOR:
Comprehensive Cancer Trials Unit, Department of Clinical Oncology, The Chinese University of Hong Kong

TITLE:
NEO-SPACE trial:
Neoadjuvant Pembrolizumab-Gemcitabine-Ci**s**platin followed by Concurrent **P**embrolizumab-Chemoradiation and Maintenance Pembrolizumab for Stage IV**A** Nasopharyngeal **C**anc**e**r

Lead Principal Investigator
Prof Anthony Tak Cheung Chan
Department of Clinical Oncology
Prince of Wales Hospital
Sir YK Pao Center for Cancer
The Chinese University of Hong Kong
30-32 Ngan Shing Street, Shatin, Hong Kong
Tel: (852) 3505 1042/ Fax (852) 2632 5816
anthony@clo.cuhk.edu.hk

Co-Principal Investigator
Dr Darren Wan-Teck Lim
National Cancer Centre Singapore
11 Hospital Drive
Singapore 169610
darren.lim.w.t@singhealth.com.sg

Co-Principal Investigator
Dr Edwin Pun Hui
Comprehensive Cancer Trials Unit
Department of Clinical Oncology
Prince of Wales Hospital
Sir YK Pao Center for Cancer
The Chinese University of Hong Kong
30-32 Ngan Shing Street, Shatin, Hong Kong
Tel: (852) 3505 1042/ Fax (852) 2632 5816
huipun@ cuhk.edu.hk

Co-Principal Investigator
Dr. Yoke-Lim Soong
National Cancer Centre Singapore
11 Hospital Drive
Singapore 169610
Soong.yoke.lim@Singhealth.com.sg

Co-Principal Investigator
Dr Darren Ming Chun POON
Department of Clinical Oncology
Prince of Wales Hospital
Sir YK Pao Center for Cancer
The Chinese University of Hong Kong
30-32 Ngan Shing Street, Shatin, Hong Kong
Tel: (852) 3505 1042/ Fax (852) 2632 5816
pmc754@ha.org.hk

TABLE OF CONTENT

1.0 TRIAL SUMMARY

Abbreviated Title	NEO-SPACE trial: Pembrolizumab and chemoradiation in nasopharyngeal cancer
Trial Tracking Number	MISP 56746
Trial Phase	Phase 2
Clinical Indication	Previously untreated stage IVA nasopharyngeal cancer
Trial Type	Interventional
Type of control	Historical control
Route of administration	Intravenous
Trial Blinding	Unblinded, Open label
Treatment Groups	Single arm: Neoadjuvant pembrolizumab-gemcitabine-cisplatin followed by concurrent pembrolizumab-cisplatin-radiation and then maintenance pembrolizumab
Number of trial participants	46 subjects
Estimated enrollment period	18 months
Estimated duration of trial	36 months
Duration of Participation	24-36 months
Estimated average length of treatment per patient	Total 51 weeks for 17 doses of pembrolizumab: o Neoadjuvant pembrolizumab-chemotherapy: 6 weeks (2 doses of pembrolizumab) o Concurrent pembrolizumab-chemoradiation: 9 weeks (3 doses of pembrolizumab o Maintenance pembrolizumab: 36 weeks (12 doses of pembrolizumab)

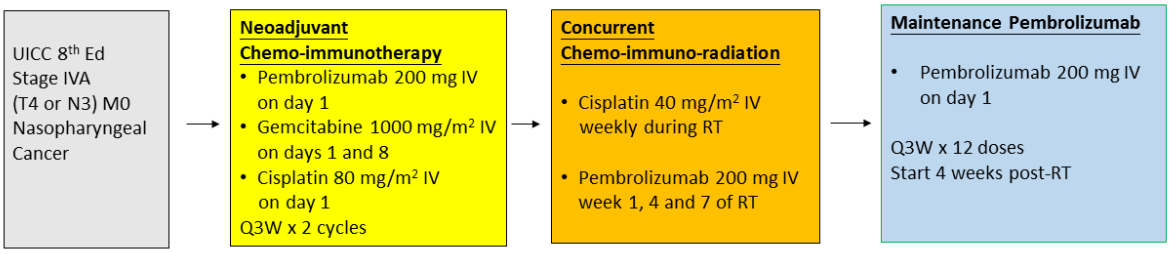
2.0 TRIAL DESIGN

2.1 Trial Design

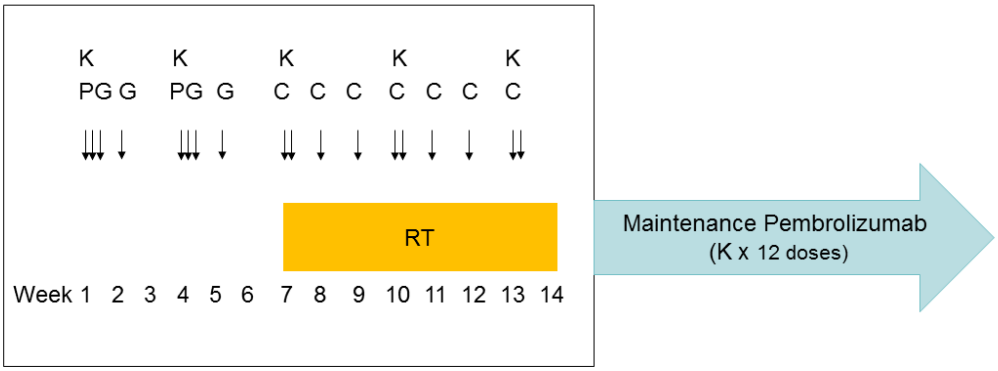
This is an open label, single arm, non-randomized, multi-site, phase 2 clinical trial of neoadjuvant pembrolizumab in combination with gemcitabine-cisplatin for 2 cycles, followed by concurrent pembrolizumab-cisplatin-radiation, and then maintenance pembrolizumab monotherapy given every 3 weeks for a total treatment duration of 12 months, in previously untreated stage IVA (UICC 8th Edition) nasopharyngeal cancer (NPC).

2.2 Trial Diagram

Sequential Treatment Schema



Treatment Plan



K: Pembrolizumab (Keytruda, Q3W)
G: Gemcitabine (D1 and D8, Q3W)
P: Cispaltin (Q3W)
C: Cisplatin (weekly)
RT: Radiotherapy

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:**

To evaluate the efficacy of incorporating pembrolizumab into standard chemoradiation protocol in locally advanced, stage IVA NPC.

Hypothesis:

Pembrolizumab in combination with 2 cycles of neoadjuvant gemcitabine and cisplatin chemotherapy followed by concurrent pembrolizumab-cisplatin-radiation and then maintenance pembrolizumab for total treatment duration of one year improves progression free survival compared to patients treated with current standard treatment in stage IVA NPC.

3.2 Secondary Objective & Hypothesis

(1) **Objective**:

To determine the overall safety, tolerability, one- and two-year rates of distant metastases, loco-regional progression, second primary cancers, and overall survival for Stage IVA nasopharyngeal carcinoma treated with induction pembrolizumab-cisplatin-gemcitabine chemotherapy followed by concurrent pembrolizumab-cisplatin-radiation and then maintenance pembrolizumab for total treatment duration of 12 months.

Hypothesis:

The sequential strategy of neoadjuvant pembrolizumab-cisplatin-gemcitabine chemotherapy followed by concurrent pembrolizumab-cisplatin-radiation and then maintenance pembrolizumab for total treatment duration of 12 months is feasible, reduces distant metastases, and improves local-regional control and overall survival, without increase in second primary cancer or death, compared to patients treated with current standard treatment in stage IVA NPC.

3.3 Exploratory Objective

(1) **Objective:**

To evaluate potential tissue and blood biomarker predictive of clinical outcome.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its

interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Pembrolizumab (Keytruda®) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator Brochure.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (1). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (2, 3).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (4, 5).

The structure of murine PD-1 has been resolved (6). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (5, 7-9). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (10, 11). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in nasopharyngeal cancer (NPC).

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Nasopharyngeal cancer (NPC) is a predominantly Asian disease, with approximately 80% of the world's 86000 cases occurring in Asian countries (12). With advances in radiation technology such as intensity modulation radiotherapy (IMRT), local and nodal control exceeds 85-90% in most reported series. Distant metastasis remains the main mode of failure, particularly in locally advanced NPC. As an example, in a study by Pan et al (13), 5 years local and nodal control of 86% and 89% was achieved with concurrent chemo-IMRT respectively, but distant failure free survival of 77% and 72% was reported for patients with T4 and N3 disease respectively (AJCC 8th edition).

Current strategies to reduce distant metastasis, including the use of adjuvant chemotherapy have been inconclusive. One major disadvantage of adjuvant chemotherapy following the completion of chemoradiation is that approximately half of patients are unable to complete the full 3 cycles of adjuvant chemotherapy, due to treatment related toxicities. The use of induction chemotherapy has two potential benefits: the first is to downsize the tumour, making radiotherapy more tolerable; the second, it allows for patients to be able to complete the chemotherapy before the onset of chemoradiation associated toxicities.

There are at least two studies now supporting the use of induction chemotherapy. A recent publication by Ma et al (14), showed the addition of induction docetaxel, cisplatin and fluorouracil prior to concurrent chemoradiation resulted in 8% improvement (80% vs 72%) in 3-year failure-free survival. Similarly, Cao et al showed that 2 cycles of cisplatin and fluorouracil prior to chemoradiation improved the 3 years disease free survival in patients (15).

Gemcitabine and cisplatin has been shown to be more effective than 5-FU plus cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (16). There are currently no studies looking at the addition of anti-PD-1 monoclonal antibody such as pembrolizumab either in the in the induction or maintenance setting. Hence, we are proposing the use of pembrolizumab in combination with 2 cycles of gemcitabine and cisplatin chemotherapy followed by concurrent chemoradiation. Following completion of chemoradiation, patients will receive maintenance pembrolizumab for total treatment duration of one year. The main objective of this Phase II study is to test the safety, efficacy and tolerability of this combination in the setting of locally advanced NPC (limited to T4 or N3, stage IVA by UICC 8th edition), as this group has the greatest risk of recurrence after the current standard treatment.

Preliminary evidence supporting the clinical efficacy of pembrolizumab monotherapy in NPC came from the KEYNOTE-028 trial, which was a global, nonrandomized, multi-cohort, phase Ib trial of pembrolizumab in patients with PD-L1-positive advanced solid tumors (17). Key eligibility criteria for the NPC cohort included unresectable or metastatic disease, failure on prior standard

therapy, and PD-L1 expression in 1% or more of tumor cells or tumor-infiltrating lymphocytes. Patients received pembrolizumab 10 mg/kg every 2 weeks up to 2 years or until disease progression or unacceptable toxicity. In the initial report, twenty-seven NPC patients was evaluated. Median age was 52.0 years (range, 18 to 68 years); 92.6% received prior therapies for recurrent or metastatic NPC; 70.4% had received three or more therapies. Partial response and stable disease were observed in seven and 14 patients, respectively, for an ORR of 25.9% (95% CI, 11.1 to 46.3) over a median follow-up of 20 months. Drug-related adverse events that occurred in 15% or more of patients included rash (25.9%), pruritus (25.9%), pain (22.2%), hypothyroidism (18.5%), and fatigue (18.5%). Grade ≥ 3 drug-related adverse events occurred in eight patients (29.6%), and there was one drug-related death (sepsis). It was concluded that pembrolizumab demonstrated antitumor activity and a manageable safety profile in patients with recurrent or metastatic NPC.

4.2.2 Justification for Dose

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

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated

saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

4.2.3 Preliminary Safety Data for the Proposed Combination Regimens

A phase 1b basket trial of pembrolizumab plus chemotherapy in patients with advanced cancer (PembroPlus) reported that standard dose pembrolizumab can be safely combined with gemcitabine, gemcitabine plus nab-paclitaxel, gemcitabine plus vinorelbine, irinotecan, and liposomal doxorubicin. In this study, pembrolizumab (2 mg/kg) was administered intravenously over 30 minutes every 21 days and infused prior to the assigned chemotherapy arm. There was no signal of increased immune-related adverse events, and dexamethasone pre-medication administered before systemic chemotherapy appear to decrease the frequency of high grade adverse events (18).

Nivolumab, another anti-PD1 check point inhibitor, has been combined with gemcitabine-cisplatin, pemetrexed-cisplatin or paclitaxel-carboplatin given for 4 cycles followed by nivolumab monotherapy in CheckMate 012, a phase 1, multi-cohort study (19). The reported safety profile was consistent with that expected for individual agents. Discontinuation related to adverse events appeared greater with the combination. The observed frequencies of immune-related adverse events affecting skin, gastro-intestine, renal, and pulmonary organs was greater than expected with single agent nivolumab. However, these treatment-related adverse events were effectively managed with corticosteroid or infliximab and did not lead to any deaths. Chemotherapy and nivolumab were associated with a risk of pneumonitis; however, discontinuation as a result of treatment related pneumonitis occurred only during nivolumab monotherapy. These results suggested that corticosteroid premedication administered for chemotherapy during the combination cycles may have prevented or partially treated pneumonitis, which worsened during nivolumab monotherapy when no regular corticosteroid premedication was given.

In a phase I/II study of pembrolizumab with gemcitabine in patients with previously treated advanced non-small cell lung cancer, pembrolizumab 200 mg IV D1 and gemcitabine 1250 mg/m^2 IV D1 and D8 every 3 weeks was considered feasible for on-going phase 2 evaluation (20). In patients with platinum-treated metastatic urothelial cancer, pembrolizumab 200 mg IV every 3 week plus either full dose gemcitabine (1000 mg/m^2 D1 and D8) or docetaxel was found to be feasible with encouraging anti-tumor activity (21).

KeyNote-059 studied the efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal cancer. In cohort 2, pembrolizumab (200 mg Q3w) was combined with cisplatin (80 mg/m2 Q3W) and either 5FU or capecitabine. In the preliminary report of 25 patients, the overall response rate was 60% with acceptable safety profile (22)

In the randomised, phase 2 cohort of the open-label KEYNOTE-021 study, the combination of pembrolizumab, carboplatin and pemetrexed achieved superior response rate and progression survival with similar rate of adverse events compared to carboplatin and pemetrexed alone (23). In the phase 3 KEYNOTE-189 trial, the addition of pembrolizumab to carboplatin and pemetrexed resulted in significantly longer overall survival and progression-free survival than chemotherapy alone, without increase in adverse events. Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group (24).

Powell et al presented preliminary report on the safety of pembrolizumab with chemoradiation in locally advanced squamous cell carcinoma of head and neck at ASCO 2017. Pembrolizumab can be safety delivered with weekly cisplatin and radiation in head and neck cancer with no new toxicity signals seen (25).

Pembrolizumab in combination with cisplatin and gemcitabine is being studied in the following on-going clinical trials:

- Phase Ib/II Study of Neoadjuvant Pembrolizumab With Gemcitabine-Cisplatin (Cisplatin-Eligible) or Gemcitabine (Cisplatin-Ineligible) in Subjects With T2-4aN0M0 Urothelial Cancer: HCRN GU14-188 (ClinicalTrials.gov: NCT02365766).

- Phase II Single Arm Study of Gemcitabine and Cisplatin Plus Pembrolizumab as Neoadjuvant Therapy Prior to Radical Cystectomy in Patients With Muscle-Invasive Bladder Cancer (ClinicalTrials.gov: NCT02690558)

- A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab With or Without Platinum-Based Combination Chemotherapy Versus Chemotherapy in Subjects With Advanced or Metastatic Urothelial Carcinoma (ClinicalTrials.gov: NCT02853305)

4.2.4 Rationale for Endpoints

The baseline rates used in this study are based upon the completed phase II studies of RTOG 0615 bevacizumab-cisplatin-RT (26) and cetuximab-cisplatin-RT (27).

The primary efficacy endpoint will focus on 2-year progression free survival. This will include both local progression and distant metastasis, which were the major failure for T4 and N3 disease respectively. The progression and survival rates in this study will be compared with the historical rates from previous publications.

Since there is limited experience with the incorporation of pembrolizumab into sequential neoadjuvant-concurrent chemoradiation followed by maintenance pembrolizumab regimen, this study will determine whether the full regimen can be delivered per protocol prescription and is safe. A two stage design with an interim safety analysis after accrual of the first 14 subjects will be adopted. There is particular concern with the incidence in NPC patients receiving curative intent of chemoradiation schedule with increased rate of grade 4 mucositis or skin reaction, which were the dose-limiting toxicity for head and neck radiation and could potentially be aggravated after incorporation of pembrolizumab into standard chemoradiation protocol. Therefore, the incidence of patients with either grade 4 mucositis/skin reaction or any grade 5 adverse event attributed to the protocol treatment will be used to evaluate safety. The incidence of these events will be examined in the first year from the start of treatment and then beyond the first year.

Patient tolerability will be evaluated in terms of protocol treatment delivery. The protocol treatment regimen will be considered as 3 treatment components (neoadjuvant, concurrent and maintenance components) for tolerability assessment.

4.2.4.1 Efficacy Endpoints

Primary efficacy endpoint:

-Two-year progression free survival

Secondary Endpoints

-Grade 4 mucositis/skin reaction or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to protocol treatment during the first year

-Grade 4 mucositis/skin reaction or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to protocol treatment occurring *after* the first year;

-Patient tolerability to each component (neoadjuvant, concurrent and maintenance part) of the protocol treatment regimen;

-Other ≥ Grade 3 adverse events;

-Death during or within 30 days of discontinuation of protocol treatment;

-One- and two-year distant metastases rates;

-One- and two-year local-regional progression rates;

-One- and two-year second primary rates;

-One- and two-year overall survival rates.

4.2.4.2 Biomarker Research

Rationale for measuring PD-L1 expression

PD-L1 expression is the most extensively studied biomarker with respect to predicting the efficacy of anti–PD-1 or anti–PD-L1 therapies. In pembrolizumab trials for melanoma and non–small-cell lung cancer (NSCLC), high PD-L1 positivity in tumor cells was strongly correlated with tumor response and survival. However, such a correlation was observed in HNSCC only when PD-L1 staining in immune cells was included (28). In the phase Ib trial of pembrolizumab (KEYNOTE-028) which only enrolled patients with PD-L1–positive tumor, pembrolizumab demonstrated antitumor activity and a manageable safety profile in patients with recurrent or metastatic NPC (RM-NPC) (17). A randomized phase III study of pembrolizumab in patients with platinum-pretreated RM-NPC, irrespective of PD-L1 status, is currently recruiting patients (ClinicalTrials.gov NCT02611960) and will help to define the efficacy of pembrolizumab in patients with PD-L1–negative NPC. In a recent phase 2 trial of nivolumab in RM-NPC, there was no significant statistical association between PD-L1 expression in tumor and/or immune cells with survival or response. However, a higher proportion of objective responses were observed in patients with PD-L1-positive (> 1% expression) than those with PD-L1 negative tumors. Furthermore, responders who experienced a greater 'depth' of tumor shrinkage have PD-L1-positive tumors. The complete responder in that study possessed the highest level of PD-L1 expression in the immune cells (29). Therefore further study on the relationship of PD-L1 status and treatment outcome in previously untreated NPC cohort is warranted.

Rationale for measuring plasma EBV DNA

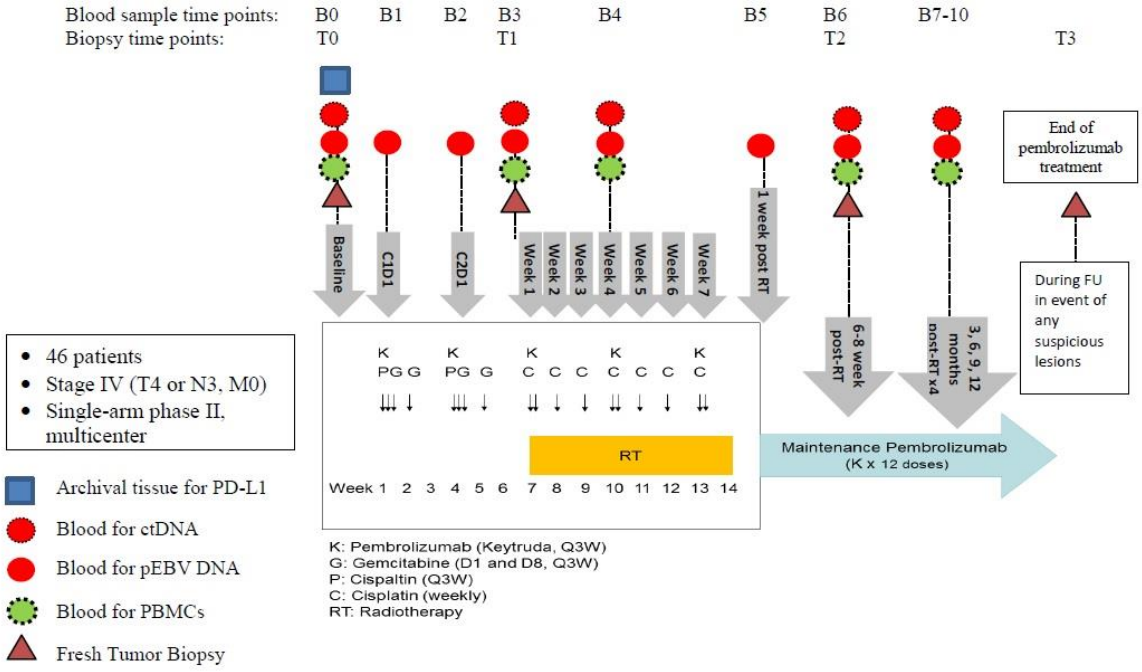
Pre-treatment plasma EBV DNA has been shown to correlate with cancer stage, clinical outcome and prognosis in NPC (30-32). Post-RT plasma EBV DNA has even better correlation with prognosis and has been used to monitor recurrence during post-treatment surveillance (33, 34). Elevated plasma EBV DNA has been shown to predate clinical recurrence by 3 to 7 months (35). Detectable or high level of post-RT plasma EBV DNA can predict a poor progression-free or overall survival when compared with those with undetectable or low EBV DNA level, and represent a biomarker of subclinical residual disease (33). In a phase II prospective study on 31 loco-regionally advanced nasopharyngeal carcinoma patients who underwent neoadjuvant chemotherapy followed by concurrent chemoradiation, plasma EBV DNA was obtained at baseline, weekly during treatment, 4-6 weeks post-treatment, and q2 months for one year after treatment. Plasma EBV DNA level was found to be increased significantly in 8 of 9 patients who experienced treatment failure. Patients who had no evidence of disease did not experience elevated serum EBV DNA levels (33).

Given the above results, we will collect blood for plasma EBV DNA analysis at several specified time points for this current study.

Rationale for Translational Research:

As the field of biomarker research in immune-oncology is evolving, there is as yet no standardized biomarker to predict the response to immune checkpoint inhibitors. We will prospectively collect tissue and blood samples to study immune related biomarkers. Tumor tissues will be obtained before and after neoadjuvant therapy, and post-RT. Plasma and immune cells will be isolated at study entry, post-neoadjuvant therapy, post-RT, during maintenance pembrolizumab and at the end of study.

Tissue and blood samples collection schema:



- Time point for fresh tumor biopsy:

  T0 – stands for timepoint 0 and is the baseline tumor biopsy (before C1D1)

  T1 – stands for timepoint 1 and is the tumor biopsy after C2D1 neoadjuvant chemo (before RT)

  T2 – stands for timepoint 2 and is the tumor biopsy at 6-8 weeks after completion of RT

  T3 – stands for timepoint 3 and is the tumor biopsy at any time during or after treatment completion when suspected recurrent or metastatic lesion present

- Time point for blood sample collection:
    - B0 – Baseline
    - B1 – Cycle 1 Day 1
    - B2 – Cycle 2 Day 1
    - B3 – Week 1(before RT)
    - B4 – Week 4
    - B5 – 1week post RT
    - B6 – 6-8 weeks post RT
    - B7-B10 – 3, 6, 9 and 12 months post RT (x4) (allow window of ± 7 days for 3 month post-RT, and ± 10 days for time points of 6 months and beyond)

1) **Baseline Archival Tumor Tissue Collection**

All subjects should submit either a newly obtained core or excisional biopsy or archival tissue (FNA not adequate for both archival and new tissue samples) to a central lab for characterization of PD-L1 status.

2) **Fresh Tumor Biopsy Collection**

a) 1 core of tissue: Fixed in Formalin for Paraffin Embedding (FFPE) for immunohistochemistry (IHC) study

b) 1 core of tissue: Fresh in Hypothermosol or frozen in freezing media for single cell RNA sequencing (scRNAseq) study

c) 1 core of tissue: fresh frozen sample for bulk RNA/ TCR sequencing study

3) **Blood Sample Collection**

a) BD Vacutainer CPT with Sodium Citrate (8 mL x 2): for peripheral blood mononuclear cells (PBMC) isolation.

b) K_2EDTA Tubes for plasma DNA collection (5 mL x 1 for pEBV DNA alone; 9 ml x2 when collect for both pEBV DNA and ctDNA).

The collected cells will be utilized for downstream profiling and functional experiments, including but not limited to RNA-sequencing (bulk and/or single cell), whole exome or DNA sequencing, TCR/BCR sequencing, Total-seq, flow cytometry, mass cytometry, and/or cell line generation for monocellular and/or co-culture experiments (e.g. organoids/tumoroids, fibroblasts, immune cells). Cell lines may be frozen down for long term storage at MSD or CUHK for future research purposes.

Refer to Operations Manual for technical details.

Estimated blood collection volume:

	Blood sample time point and volume (ml)										
Blood sample type	**B0**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**
ctDNA	18	-	-	18	18	-	18	18	18	18	18
pEBV DNA	-	5	5	-	-	5	-	-	-	-	-
PBMC	16	-	-	16	16	-	16	16	16	16	16
Total volume (mL)	**34**	**5**	**5**	**34**	**34**	**5**	**34**	**34**	**34**	**34**	**34**

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of nasopharyngeal carcinoma (from primary lesion and/or lymph nodes) of WHO type II-III histology type will be enrolled in this study.

2. NPC associated with EBV infection, determined as:

    a. The presence of EBV has been confirmed in the tumour by immunohistochemistry for EBV antigens or in situ hybridization for EBV early RNA (EBER), or

b. NPC occurred in association with a raised serum titre of IgA to EBV viral capsid antigen (VCA) or early antigen (EA) in a patient living in endemic area of high incidence of EBV+ undifferentiated NPC, or

c. NPC in the context of an elevated circulating EBV genome level

3. AJCC 8th edition Stage IVA (i.e any T4 or any N3) based on the following diagnostic workup:
   a. Evaluation of tumor extent with MRI of the nasopharynx and neck. If MRI is medically contraindicated, CT scan with ≤ 3 mm and intravenous contrast is acceptable.
   b. Distant metastasis staging:
      i. CT scan with contrast of the chest, abdomen, and pelvis or a total body PET/CT scan;
      ii. Bone scan, if a PET/CT scan is not performed.

4. A male participant must agree to use contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days plus an additional 120 days (a spermatogenesis cycle) for study treatments with evidence of genotoxicity at any dose after the last dose of study treatment and refrain from donating sperm during this period.

5. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days plus 30 days (a menstruation cycle) for study treatments with risk of genotoxicity after the last dose of study treatment.

6. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

7. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

   Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut.

8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation/randomization.

9. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL [a]
Renal	
Creatinine OR Measured or calculated [b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR >50 mL/min for participant with creatinine levels >1.5 × institutional ULN
Proteinuria	< 2+ by dipstick urinalysis If dipstick is ≥ 2+, then 24 hr urine protein must be < 1.0 g or urine protein creatinine ratio (UPC) must be < 1
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

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

[b] Creatinine clearance (CrCl) should be calculated per the Cockcroft-Gault equation.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to first dosing (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Note: in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

3. Has received any prior systemic anti-cancer therapy including investigational agents.

4. Has received any prior radiotherapy.

5. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

7. Has a known additional malignancy. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

8. Has known active CNS metastases and/or carcinomatous meningitis.

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

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

11. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

12. Has an active infection requiring systemic therapy.

13. Has a known history of Human Immunodeficiency Virus (HIV). *Note: No HIV testing is required unless mandated by local health authority.*

14. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Subjects who have been treated and now have a viral load that is undetectable are eligible.

15. Has a known history of active TB (Bacillus Tuberculosis).

16. Has prior solid organ transplant or bone marrow transplant.

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

18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to MSD within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to MSD. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to MSD and followed as described in Section 7.2.2.

5.1.5 Use in Nursing Women

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

5.2 Trial Treatments

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned. The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Neoadjuvant phase (pembrolizumab-gemcitabine-cisplatin):					
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Gemcitabine	1000 mg/m^2	Q3W	IV infusion	Days 1 and 8 per 3 week cycle	Experimental
Cisplatin	80 mg/m^2	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Note: - For two cycles. - Pembrolizumab will be administered prior to chemotherapy when both agents are delivered on the same day. -Body surface area (BSA) should be calculated by Du Bois formula.					
Concurrent phase (pembrolizumab-cisplatin-radiation):					
Pembrolizumab	200 mg	Q3W	IV infusion	Week 1, 4 and 7 of IMRT	Experimental
Cisplatin	40 mg/m^2	Q1W	IV infusion	Weekly from week 1 to 7 of RT	Standard of care
Radiation (refer to section 5.2.3)					Standard of care
Note: - Cisplatin: 40 mg/m^2/day, weekly during radiation, with a maximum cumulative dose of 280 mg/m^2. - Pembrolizumab will be administered prior to chemotherapy when both agents are delivered on the same day. - Body surface area (BSA) should be calculated by Du Bois formula.					
Maintenance phase (pembrolizumab monotherapy)					
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Note: - Start 4 weeks after last dose of RT. - Continue for total of 12 doses					
Note: Pembrolizumab will be given for 2 doses in neoadjuvant phase, 3 doses in concurrent phase, and 12 doses in maintenance phase, for total of 17 doses.					

General requirements for initiation of each chemotherapy cycle

- ECOG Performance status < 3;
- CBC/differential and chemistries obtained within 1 day prior to beginning chemotherapy, with adequate bone marrow function defined as follows: Absolute Neutrophil Count (ANC) ≥ 1,000 cells/mm3 and Platelets ≥ 100,000 cells/mm3;
- AST/ALT and total bilirubin < grade 2 (CTCAE, v. 4);
- Serum creatinine < grade 2 (CTCAE, v. 4);
- All AEs must be < grade 3 (CTCAE, v. 4).

General requirement for initiation of each pembrolizumab dose

Pembrolizumab should be withhold for immune-related adverse events (AEs) of grade 2 or above that is *possibly* associated with pembrolizumab (refer to Table 3).

Exceptions are:
- Laboratory values that do not have any clinical correlate (eg, amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis).
- Nausea and vomiting controlled by medical therapy.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

Administration guideline for high-dose cisplatin (in cisplatin-gemcitabine regimen)

High dose cisplatin is highly emetogenic. Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below. This may need to be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen for this combination is to be determined by the local investigator.

- High-Dose Cisplatin Anti-Emetic Administration Guidelines: Substance P antagonist such as aprepitant, 125 mg PO on day 1 prior to cisplatin and 80 mg on days 2 and 3. 5-HT3 antagonists (e.g. ondansetron, 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin. Dexamethasone x 3 days prior to cisplatin, 12 mg PO or IV on day 1 and 8 mg on days 2 and 3. Use of other anti-nausea meds such as metoclopramide, lorazepam, olanzapine, or prochlorperazine is left to the discretion of the investigator.

- Cisplatin Pre-Hydration Guidelines: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.

- Cisplatin Administration: Cisplatin, 80 mg/m2 over 60-120 minutes IV in 250 cc NS. See section 5.2.2 for guideline on dose modifications.

• Cisplatin Post-Hydration Guidelines: Following the end of the cisplatin administration, at least an additional 1.5 liters of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2-4 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

Administrative guideline for gemcitabine

The preparation and administration of gemcitabine should follow local treatment guidelines. Pre-medication with steroids prior to IV infusion is permitted as per local standard of care. However, the following recommendations should be taken into account.

Gemcitabine infusion: 1000 mg/m^2 in 250 ml NS over 30 minutes on days 1 and 8 of a 3-week cycle.

Note: The final concentration of the prepared drug must be in the range of 38 mg/ml to 0.1 mg/ml.

Myeloid growth factor use during neoadjuvant chemotherapy

Pegfilgrastim or Filgrastim may be used according to institutional guidelines. We recommend following the NCCN myeloid growth factor use guidelines (see NCCN.org). However, there is lack of evidence on the combined use of myeloid growth factor and pembrolizumab.

Note: Hematologic growth factors for neutropenia or anemia are not allowed during *concurrent cisplatin and radiation* treatment.

Administration guidelines for low-dose cisplatin concurrent with radiation

No concurrent cisplatin will be administered after the final week of radiation, but the final dose of cisplatin may be administered following the last dose of radiation if it is administered within the same calendar week. Investigators should strive to administer cisplatin on the same day each week but variance of 1 day is acceptable for vacations, holidays, etc. If radiation treatments are held for toxicity, cisplatin dosing should also be held.

High dose cisplatin is highly emetogenic. While this protocol is using an intermediate dose of cisplatin (40mg/m^2) when administered concurrently with radiation, investigators should be prepared to use aggressive prophylactic antiemetics and hydration. Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below. This may need to be modified based on local guidelines

and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen for this combination is to be determined by the local investigator.

- Low-dose Cisplatin anti-emetic administration guidelines: 5-HT3 antagonists (e.g. ondansetron 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin weekly. Dexamethasone x 3 days starting prior to the cisplatin dose weekly, 12 mg on day 1 and 8 mg on days 2 and 3 each week. Use of other anti-nausea meds such as aprepitant, metoclopramide, or prochlorperazine is left to the discretion of the investigator.

- Low-dose Cisplatin pre-hydration guidelines: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.

- Low-dose Cisplatin administration: Cisplatin, 40 mg/m2 over 30-60 minutes IV in 250 cc NS. See Section 7.9 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.

- Low-dose Cisplatin post-hydration guidelines: Following the end of the cisplatin administration, an additional liter of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

Administration Guideline for Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Pembrolizumab will be administered prior to chemotherapy when both agents are delivered on the same day (18, 23).

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

5.2.2 Dose Modification

Dose Modification for neoadjuvant cisplatin-gemcitabine

Cisplatin Dose Levels During Neoadjuvant Cisplatin-Gemcitabine		
Starting Dose	Dose Level -1	Dose Level -2
80 mg/m^2	60 mg/m^2	45 mg/m^2

Substitution of carboplatin for cisplatin is permitted in the case if either renal or ototoxicity as defined below. Investigators may choose to substitute carboplatin for cisplatin according to the following parameters:

See section above and parameters in below sections for situations in which carboplatin substitution for cisplatin is permitted during neoadjuvant cisplatin-gemcitabine		
Carboplatin Dose Levels during neoadjuvant chemotherapy		
Carboplatin Starting Dose	**Carboplatin Dose Level -1**	**Carboplatin Dose Level -2**
AUC 5	AUC 4	AUC 3

Gemcitabine Dose Levels During Neoadjuvant Cisplatin-Gemcitabine		
Starting Dose	Dose Level -1	Dose Level -2
1000 mg/m^2	800 mg/m^2	600 mg/m^2

Cisplatin Dose Modifications for Hematologic Adverse Events during Neoadjuvant Cisplatin-Gemcitabine

Chemotherapy should not be administered until the ANC is at least 1000 cells/mm^3 and the platelet count is at least 100,000/mm^3. If these parameters are not met, then treatment should be delayed in weekly increments until they have recovered to this level, but no more than a 21-day delay is permitted.

Dose reductions for ANC and platelets based on counts at anticipated day of treatment, ONCE RECOVERY TO THE ABOVE LEVELS ARE ACHIEVED:

ANC		Platelets	Reduction
At least 1000 mm^3	and	At least 100,000	None
< 1000 mm3	or	< 100,000	One dose level of BOTH cisplatin and gemcitabine

Cisplatin Dose Modifications for Non-Hematologic Adverse Events during neoadjuvant cisplatin-gemcitabine

Neurological Events Attributable to Cisplatin (e.g. peripheral neuropathy): Grade 2, decrease cisplatin by one dose level. ≥ grade 3, hold cisplatin.

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from fluid in the Eustachian tube. Because no AE scale, including the CTCAE v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held, and for grade 2 clinical hearing loss, one dose level reduction.

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance > 50. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen)

Cisplatin dose modifications for creatinine during neoadjuvant cisplatin-gemcitabine			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	> 50	No change
> 1.5	and	40-50	One dose level

Substitution of carboplatin for cisplatin is permitted in the case if either renal or ototoxicity as defined below. Investigators may choose to substitute carboplatin for cisplatin according to the following parameters:

Carboplatin substitution for cisplatin during neoadjuvant cisplatin-gemcitabine for renal toxicity			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction

≤ 1.5	or	≥ 50	Use cisplatin
> 1.5	and	40-50	May substitute carboplatin at AUC 5
		< 40	

Carboplatin substitution for cisplatin during neoadjuvant cisplatin-gemcitabine for ototoxicity	
Clinical grade hearing loss	Cisplatin dose reduction
0, 1 or 2	Use cisplatin
3 or greater	May substitute carboplatin at AUC 5

Dose Modification Guidelines for Gemcitabine Hematologic Drug-Related Events

Dose reduction for day 8 gemcitabine			
ANC (x10^6/L)		**Platelet count**	**Gemcitabine Dose**
≥1.0	and	≥ 100	100%
0.5 – 0.99	or	50 – 99	75%
< 0.5	or	<50	Hold

Note: Day 1 of Gemcitabine may be delayed; however, held doses of gemcitabine on day 8 will be considered missed doses and will not be delayed or made up.

Dose Modification Guidelines for Gemcitabine Non-Hematologic Drug-Related Events

Withhold gemcitabine or reduce dose by 50% of full dose for other severe (Grade 3 or 4) non-hematologic toxicities until resolved to Grade 0-1.

- No dose modifications are recommended for alopecia, nausea, or vomiting.
- Permanently discontinue gemcitabine for the following:
- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome

- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

For additional guidance regarding treatment modification of gemcitabine, please refer to the United States package insert (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities

All Other Non-Hematologic Adverse Events During neoadjuvant cisplatin-gemcitabine

For grade 3 or 4 events, drugs should be held until resolution to grade 1 or less, then both drugs resumed at dose level -1. Gemcitabine doses on day 8 of each cycle will not be made up but merely skipped for grade 3 or greater AEs occurring between days 1 and 8. Neoadjuvant treatment should be stopped if greater than grade 2 AEs are not resolved to grade 1 within 3 weeks, and patient should proceed directly to next phase of treatment. For specific AEs clearly attributable exclusively to one or the other agent (cisplatin or gemcitabine), one level dose reduction only for that agent is required.

Cisplatin dose modification during concurrent radiation

Note: If adverse events prevent the administration of cisplatin during radiation, the patient may continue to receive pembrolizumab and radiation therapy.

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to CTCAE, v. 4 while receiving concurrent cisplatin with radiotherapy.

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy attributable AEs requiring a break in treatment, resumption of concurrent cisplatin may begin when AEs have recovered to the levels specified below. If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment, treatment off protocol can continue according to the judgment of the treating physician.

There will be no dose re-escalation for concurrent cisplatin.

Chemotherapy dosage modifications are based upon laboratory values obtained within the 24 hours prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

The dose modifications for cisplatin (below) are intended to be permanent (i.e., if the patient's dose is reduced to dose level -1, it remains at the reduced dose level).

Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Starting Dose	Dose Level -1	Dose Level -2

40 mg/m^2	30 mg/m^2	23 mg/m^2

Chemotherapy must not be administered until the ANC is ≥ 1,000 and platelets are ≥ 100,000. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

ANC		Platelets	Reduction
≥ 1000 mm^3	and	≥ 75,000	None
< 1000 mm^3	or	< 75,000	One dose level

Note: Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.

Substitution of carboplatin for cisplatin is permitted in the case if either renal or ototoxicity as defined below. Investigators may choose to substitute carboplatin for cisplatin according to the following parameters:

See section above and parameters in below sections for situations in which carboplatin substitution for cisplatin is permitted during concurrent chemoradiation		
Carboplatin Dose Levels during concurrent chemoradiation		
Carboplatin Starting Dose	**Carboplatin Dose Level -1**	**Carboplatin Dose Level -2**
AUC 2	AUC 1.5	AUC 1

If carboplatin has been substituted for cisplatin during neoadjuvant treatment, carboplatin substitution should continue during the concurrent treatment. DOSE REDUCTIONS TO CISPLATIN OR CARBOPLATIN DURING NEOADJUVANT PHASE NEED NOT TRANSFER TO THE CONCURRENT SETTING UNLESS THERE IS NOT RESOLUTION OF TOXICITIES.

Cisplatin Dose Modifications for Non-Hematologic Adverse Events during Concurrent Radiation

Neutropenic Fever: Temperature of 38.5°C with ANC < 1000 is an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever is noted, the chemotherapy dose reduction will be determined by the weekly blood counts. See above.

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50 ml/min. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen).

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	≥ 50	No change
> 1.5	and	40-50	One dose level
		< 40	Hold drug

Carboplatin substitution for cisplatin during concurrent chemoradiation for renal toxicity			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	≥ 50	Use cisplatin
> 1.5	and	40-50	May substitute carboplatin at AUC 2
		< 40	

Neurologic (neuropathy) adverse events:

Grade (CTCAE, v. 4)	**Dose Reduction**
0-1	None
2	One dose level
3-4	Hold drug

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale, including

the CTCAE, v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, one dose level reduction, or carboplatin substitution as specified below.

Carboplatin substitution for cisplatin during concurrent chemoradiation for ototoxicity	
Clinical grade hearing loss	Cisplatin dose reduction
0, 1 or 2	Use cisplatin
3 or greater	May substitute carboplatin at AUC 2

All Other Non-Hematologic Adverse Events Attributable to Cisplatin (or carboplatin, in the case of substitution) during Concurrent Radiation: For > grade 2, hold cisplatin (or carboplatin, in the case of substitution), re-evaluate weekly until AE grade falls to 0 or 1, then restart cisplatin at one lower dose level.

Note: Do not hold cisplatin (or carboplatin, in the case of substitution) for > grade 2 lymphopenia, hypoalbuminemia, mucositis, or dysphagia.

5.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

	Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

5.2.3 Radiotherapy

5.2.3.1 Equipment

Radiotherapy *must* be given using Intensity Modulated Radiotherapy (IMRT) techniques. This includes megavoltage equipments capable of delivering static-gantry intensity modulation beams with a multileaf collimator or dynamic intensity modulation (e.g. VMAT and Tomotherapy). Image Guided Radiotherapy (IGRT) is optional except when reduced Planning Target Volume (PTV) margins of less than 5mm are used.

5.2.3.2 Immobilisation and Localisation

Patient should have dental clearance to minimize risk of dental complications after treatment. Ideally, this should be performed prior to induction chemotherapy, as it may be difficult to schedule dental clearance once chemotherapy has commenced due to increased risk of infection.

The patient should lie on a flat top table in supine position with the neck in neutral position. Patient is immobilized with immobilization device that should at least include the head and neck, but immobilization techniques that include the shoulders is strongly recommended.

Treatment planning CT scans (with intravenous iodine contrast enhancement, unless contraindicated) of all tissues to be irradiated must be acquired with the patient in the treatment position and using the same immobilization device as for treatment to define gross target volume(s), and clinical target volume(s). Scan thickness of $\leq$ 3 mm contiguous slices is recommended, particularly through region that contains the primary tumour.

Contrast enhanced MRI scan (within 3 weeks of radiotherapy planning) is required for “T” staging and to assist in definition of target volumes unless medically contraindicated. Whenever possible, the MRI scan should be set up as close as possible to the treatment position. Image registration with planning CT scans should be performed in a region of interest encompassing the GTV, skull base, brainstem, and optic chiasm.

This procedure must be performed prior to induction chemotherapy. Radiotherapy simulation procedure will have to be repeated after Day 1 (before Day 8) of second cycle of induction

chemotherapy. This is to allow adequate time for planning so as not to delay the subsequent concurrent chemo-radiation treatment. Patients undergoing post-induction treatment planning scans should be immobilized in as similar position as possible with the pre-induction treatment position

.

5.2.3.3 Target Volumes

Gross Tumor Volume

The primary Gross Tumor Volume (GTVp) is defined as all known gross disease determined from clinical information, endoscopic findings, CT, MRI, and PET-CT. It is recommended that the GTV is contoured in collaboration with a head and neck radiologist.

Grossly positive lymph nodes (GTVn) are defined as:

- Retropharyngeal LNs >5 mm or cervical LNs >10 mm in shortest diameter (11 mm for subdigastric node)

- Three or more contiguous and confluent LNs, each with shortest diameter of 8-10 mm

- LNs of any size with central necrosis or a contrast-enhanced rim

- LNs of any size with extracapsular extension

- LNs of any size with overt FDG uptake on FDG-PET scan signifying malignant involvement

(Those LNs not fulfilling the above criteria are considered as equivocal)

Clinical Target Volume (CTV)

Primary CTV	
CTVp1 = High risk primary tumour CTV	▪ GTVp + ≥3 mm margin (0 mm if close to critical neurological structure) ▪ Whole nasopharynx (recommended but not mandatory)

CTVp2 = intermediate risk (subclinical sites)	▪ CTVp1 + 5 mm margin (1 mm if close to critical neurological structure), but to include high-risk subclinical local sites: • Whole nasopharynx (if not included in CTVp1) • Sphenoid sinus : Lower half if T1-2 : Entire sinus if T3-4 • Clivus : Anterior 1/3 if no gross clivus invasion : Whole clivus if gross invasion • Ipsilateral cavernous sinus : if T3-4 • Base of skull : lateral border of Foramen Ovale, Foramen Rotundum and Petrous tips • Nasal cavity and maxillary sinuses : posterior fourth (to ensure adequate inclusion of the pterygo-maxillary fissure and pterygo-palatine fossae) • Bilateral pterygoid fossae • Bilateral parapharyngeal spaces

Nodal CTV	
CTVn1 = High risk nodal CTV	▪ GTVn + ≥3 mm margin (consider 10mm expansion if extracapsular extension present)
CTVn2 = Intermediate risk (subclinical sites)	▪ CTVn1 + 5 mm margin ▪ For All cases - Retropharyngeal, Level II, III and Va lymph nodes, bilaterally (as defined by the cervical lymph node levels as set out in expert consensus guidelines in 2013 (Gregoire et. al.)) ▪ Ipsilateral level IB if: • there is gross level IB or II nodes on that side • structures that drain to level Ib as the first echelon site (oral cavity, anterior half of nasal cavity) ▪ This should be anatomically edited at the sternocleidomastoid muscle border as appropriate, rather than just simple geometric expansion.

CTVn3 = Low risk (subclinical sites)	▪ If nodal involvement is confined to level II nodes only, the treating radiation oncologist may include bilateral cervical lymph node levels IV and Vb (as defined by the cervical lymph node levels as set out in expert consensus guidelines in 2013 (Gregoire et. al.)) in CTVn3 so that a lower prophylactic dose can be delivered ▪ Alternatively, the treating radiation oncologist may also include the bilateral cervical lymph node levels IV and Vb under CTVn2 ▪ This should be anatomically edited at the sternocleidomastoid muscle border as appropriate, rather than just simple geometric expansion.
CTVn4 = Equivocal lymph nodes	▪ The treating Radiation Oncologist has the option of prescribing an intermediate dose of 62.7 Gy, to small volume equivocal level IB lymph to limit dose delivered to the mandible or equivocal level IV and VB lymph nodes to limit the dose delivered to the brachial plexus. ▪ GTVn + ≥3 mm margin

Pre-induction and Post-induction GTVs and CTVs

This trial involves the use of induction chemotherapy prior to definitive concurrent chemo-radiation. As much as possible, the pre-induction GTVs that can be fully covered to the full therapeutic dose without exceeding the maximal tolerance of critical OARs should be used. However, in cases where pre-induction tumours that abuts critical OARs (chiasm, brainstem and spinal cord) showed gross regression following chemotherapy, post-induction GTV at the area(s) abutting the critical OARs (chiasm, brainstem and spinal cord) may be used to avoid excessive risk of damage. It is important to ensure that the pre-induction GTV that abuts critical OARs is covered at least by CTVp2. Pre-induction base of skull involvement should be treated to full therapeutic dose (CTVp1).

Planning Target Volume (PTV)

A margin of 5 mm around the CTVs is required in all directions to compensate for the variability of treatment set up and internal organ motion. If the investigator wants to reduce the PTV margin below 5 mm, daily IGRT must be employed.

If expansion of CTVs results in PTVs that extend beyond the patient's external contour, the PTVs should be trimmed to within 5mm from the external contour. For gross disease that extends to within 5mm of external surface, the use of tissue equivalent material (bolus) is recommended.

Organs at Risk (OARs)

OARs are contoured according to the following published guidelines (36, 37):

1. Brouwer CL, Steenbakkers RJ, Bourhis J, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol. 2015 Oct;117(1):83-90. doi: 10.1016/j.radonc.2015.07.041. Epub 2015 Aug 13.

2. Sun Y, Yu XL, Luo W. Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy. Radiother Oncol. 2014 Mar;110(3):390-7. doi: 10.1016/j.radonc.2013.10.035. Epub 2014 Apr 7.

Required OARs:

• Brainstem • Spinal cord • Optic chiasm • Optic Nerve- Left and Right • Parotid – Left and Right • Parotids - Combined • Eye- Left and Right • Lens- Left and Right • Cochlea- Left and Right • Internal Acoustic Meatus- Left and Right • Temporal lobe-Left and Right	• Constrictor-Superior • Constrictor-Middle • Constrictor-Inferior • Constrictor-Cricopharyngeus • Constrictor-Esophagus • Brachial Plexus- Left and Right * • Glottic larynx • Oral cavity • Mandible • Temporo-Mandibular Joint • Pituitary • Thyroid gland

5.2.3.4 Treatment Planning

Dose Prescription

Treatment will be delivered once daily, 5 fractions per week, over 6.5 to 7 weeks (33 or 35 fractions) in accordance with department standards of care. All targets will be treated simultaneously.

	In 33 fractions (preferred)	In 35 fractions
PTV1 (CTVp1 and CTVn1 + margins)	69.96 Gy at 2.12 Gy per fraction	70 Gy at 2 Gy per fraction
PTV2 (CTVp2 and CTVn2 + margins)	59.4 Gy at 1.8 Gy per fraction	60.2 Gy in 1.72 Gy per fraction
PTV3 (CTVn1 + margins)	54.12 Gy at 1.64 Gy per fraction	56 Gy at 1.6 Gy per fraction
PTV4 (CTVn4 + margins)	62.7 Gy at 1.9 Gy per fraction	63 Gy in 1.8 Gy per fraction

Planning Priorities

The planning priorities for dose coverage and constraints will be in the following order:

1) Critical Normal Structure Constraints: Specifically, the brain stem, optic chiasm, and spinal cord, which take priority over coverage of the tumor. If the tumor extends close to optic structures, the treating physician must discuss the possibility of blindness due to radiation therapy during the Informed Consent process;
2) Dose Specifications;
3) Planning Goals: Salivary glands;
4) Planning Goals: All other normal structures.

DVH's must be generated for all OARs. Maximum doses stated below are defined as to the maximum dose for a volume of 0.03 cc.

Target volume compliance criteria			
PTV	Dosimetric parameter	Per Protocol	Acceptable Variation
PTV1	V100%	95%	90%
	D99%	≥90%	≥85%
	D0.03cc	≤115%	≤120%
PTV2	V59.4Gy (33#) or V60.2Gy (35#)	≥95%	≥90%

PTV3	V54.12Gy (33#) or V56Gy (35#)	≥95%	≥90%
PTV4	V62.7Gy (33#) or V63Gy (35#)	≥95%	≥90%

Normal Structure Constraints and Compliance Criteria			
Structure	Dosimetric parameter	Per Protocol	Acceptable Variation
Brainstem	D0.03cc	≤54Gy	≤60Gy
Spinal cord	D0.03cc	≤45Gy	≤50Gy
Optic chiasm	D0.03cc	≤54Gy	≤56Gy
Optic nerve	D0.03cc	≤54Gy	≤60Gy
Mandible/TMJ	D0.03cc	≤70Gy	≤75Gy
Brachial plexus	D0.03cc	≤66Gy	≤70Gy
Temporal lobe	D0.03cc	≤70Gy	≤75Gy
Parotid gland	Mean	≤26Gy	≤33Gy

Only the true critical structures, not the PRVs are evaluated. In overlap situations, treatment planning should attempt to balance the tradeoff between dose to the CTV and protection of the critical structure.

Recommended Constraints Criteria for Other Normal Tissues		
Structure	Dosimetric parameter	Recommended Constraints
Oral cavity (excluding PTV's)	Mean dose	≤40Gy
Each cochlea	D0.03cc	≤55Gy
	Mean dose	≤45Gy
Eyes	D0.03cc	≤55Gy
Lens	D0.03cc	≤15Gy
Glottic larynx	Mean dose	≤40Gy
Constrictor muscles	Mean dose	≤50Gy

5.2.3.5 Image Guidance for IGRT When Using Reduced Margins

Patients treated with reduced PTV margins of <5mm will require daily IGRT. This can be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images
- Linac mounted conebeam kV or MV CT images
- Linac mounted helical MV CT images (e.g. Tomotherapy)

5.2.3.6 Patient Monitoring During Radiotherapy

Weekly review

Concurrent chemo-radiation is expected to result in significant toxicities in about two third of patients. Hence, patients should be reviewed at least once a week during radiotherapy for management of acute radiotherapy toxicities. Parameters to be collected are:

- Weight
- ECOG
- Acute toxicities (CTCAE v4.0) for:
    - Dry mouth
    - Dysphagia
    - Dysgeusia
    - Pharyngolaryngeal pain
    - Oral pain
    - Hoarseness
    - Mucositis oral
    - Dermatitis radiation
    - Any other significant acute toxicities (including but not limited to fatigue, regional alopecia, hoarseness and transient ear discomfort)
    - NGT use (Yes/No)

Patients with significant weight loss (≥10% baseline) should be advised to have a nasogastric tube (NGT) insertion.

Treatment interruption

Patients with NPC are considered to be 'Category one' patients. Hence, although interruptions in radiotherapy may be necessary due to severe acute toxicities, it is strongly discouraged. The reason for and the length of any such interruption must be documented. Treatment interruptions that exceeds five normally-scheduled treatment days will be considered as a Deviation Unacceptable for the protocol.

5.3 Randomization or Treatment Allocation

This is an open label, single arm, non-randomized trial. All eligible subjects will be allocated to the single experimental treatment arm.

5.4 Stratification

There is no stratification required.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Radiation therapy not specified in the protocol

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye) is permitted.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or

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

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

5.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis

- The participant is lost to follow-up
- Administrative reasons

5.7 Participant Replacement Strategy

Subjects who withdrew consent but has not received any study related treatment is not evaluable for any of the study endpoints, and will be replaced.

5.8 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart from Screening to End of Maintenance Chemotherapy

Trial Period:	**Screening Phase**		**Treatment Cycles**											
			Induction		Concurrent							1 week post CCRT	Maintenance	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	W1	W2	W3	W4	W5	W6	W7		Q3w X 12#	3M post RT
Scheduling Window (Days):		-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 3	± 7
Administrative Procedures														
Pre-screening Consent	X													
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X												
Clinical Procedures/Assessments														
Review Adverse Events			X	X	X			X			X		X	
Full Physical Examination		X												
Directed Physical Examination			X	X	X			X			X		X	
Vital Signs and Weight		X	X	X	X			X			X		X	
ECOG Performance Status		X	X	X	X			X			X		X	
Audiogram		X												
FACT-NP		X		X										X
Radiotherapy Simulation		X		X										
Acute radiation toxicity scoring as per section 5.2.4.6					X	X	X	X	X	X	X			X

Trial Period:	**Screening Phase**		**Treatment Cycles**											
			Induction		Concurrent							1 week post CCRT	Maintenance	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	W1	W2	W3	W4	W5	W6	W7		Q3w X 12#	3M post RT
Scheduling Window (Days):		-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 3	± 7
Dental clearance	X													
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Lab test as per Table 6		X		X	X			X			X		X[4]	
Coagulation		X												
CBC d/c			D8	D8										
CBC d/c, RLFT Bone profile			X			X	X		X	X		X		
Hepatitis B Surface Antigen		X												
Pregnancy Test – Urine or Serum β-HCG		X												
Efficacy Measurements														
MRI Post Nasal Space and Neck		X		X										X
Distal Staging		X												
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood (refer to section 4.2.4.2 and 7.1.4.3)														
Archival Tissue Collection		X												
Plasma EBV DNA/ctDNA		B0	B1	B2	B3			B4				B5	B6	B7
PBMC		B0			B3			B4					B6	B7
Tumor biopsy		T0		T1 (after C2D1, before RT))									T2 (6-8 wk post-RT)	

Trial Period:	**Screening Phase**		**Treatment Cycles**										
			Induction		Concurrent							1 week post CCRT	Maintenance	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	W1	W2	W3	W4	W5	W6	W7		Q3w X 12#	3M post RT
Scheduling Window (Days):		-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 3	± 7

Notes:

1. Radiotherapy simulation procedure includes immobilization, planning CT and MRI scan as per section 5.2.4.2 and should be done within 28 days prior to commencement of induction chemotherapy.
2. Radiotherapy simulation procedure will have to be repeated after Day 1 of second cycle of induction chemotherapy. This is to allow adequate time for planning so as not to delay the subsequent concurrent chemo-radiation treatment.
3. CT Post Nasal Space and Neck may be used if MRI is medically contraindicated
4. Magnesium is only required during neoadjuvant and concurrent phase. Urinalysis and thyroid function test (FT4 and TSH) is only required to be repeated every other cycle during maintenance phase.

6.2 Study Flow Chart from End of Concurrent Chemo-radiation to 3 Years Post Treatment

Trial Period:		**Post-Treatment (time from end of chemo-radiation)**											
Title	Discontinuation	6m	12m	18m	24m	30m	36m						
Scheduling Window (Days):	At time of Discontinuation	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10
Administrative Procedures													
Post-study anticancer therapy status		X	X	X	X	X	X						
Survival Status	X	X	X	X	X	X	X						
Local Control Status	X		X		X		X						
Distal Control Status	X		X		X		X						
Second Primary Cancer			X		X		X						
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X						
Full Physical Examination	X		X		X		X						
Directed Physical Examination		X		X		X							
Vital Signs and Weight	X	X	X	X	X	X	X						
ECOG Performance Status	X	X	X	X	X	X	X						
Audiogram			X		X		X						
FACT-NP			X		X		X						
Radiotherapy Simulation													
Late radiation toxicity scoring			X		X		X						
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Lab test as per Table 6			X		X		X						

Trial Period:		**Post-Treatment (time from end of chemo-radiation)**											
Title	Discontinuation	6m	12m	18m	24m	30m	36m						
Scheduling Window (Days):	At time of Discontinuation	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10	± 10
Efficacy Measurements													
MRI Post Nasal Space and Neck			X		X		X						
Distal Staging			X		X		X						
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood (refer to section 4.2.4.2 and 7.1.4.3)													
Tumor biopsy (at any time during or after treatment completion when suspected recurrent or metastatic lesion present)	T3												
Plasma EBV DNA/ctDNA		B8-9	B10										
PBMC		B8-9	B10										

Notes:

1. CT Post Nasal Space and Neck may be used if MRI is medically contraindicated
2. Distant staging can be either CT chest/abdomen and bone scan or FDG PET-CT
3. Local or Regional Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.
4. Distant Metastasis: Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or MSDMSD for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

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

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.1.5.4 Survival Status

The investigator or qualified designee will determine patient's survival status. Date and cause of death is to be recorded. Overall survival is defined as time from allocation until death from any cause.

7.1.1.5.5 Local Control Status

Local or regional relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy. The investigator or qualified designee will determine if patient's local control status. Date of relapse, and sites (local and or regional) should be recorded

7.1.1.5.6 Distal Control Status

Distant metastasis is defined as radiological clear evidence of distant metastases (lung, bone, brain, etc.). Where possible, biopsy is recommended. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise in a patient with a smoking history. The investigator or qualified designee will determine patient's distant control status. Date of distant metastasis and sites of metastasis should be recorded.

7.1.1.5.7 Second Primary Cancer

Tumor reappearing within the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise. Where possible, biopsy is recommended to confirm second primary cancer. The investigator or qualified designee will determine patient's second cancer status. Date of diagnosis of second cancer, and site should be recorded

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment allocation at each local study site.

Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 6.1.

The outcome of screening and the reason for all screening failure should be documented.

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Details regarding administration of trial treatment are outlined in Section 5.2 - Trial Treatment.

Interruptions from the protocol specified treatment plan for greater than 3 weeks between pembrolizumab doses for non-drug-related or administrative reasons (see section 5.2.1.2 for drug-related modifications) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial treatment will be documented by the investigator and/or designated staff. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Audiogram

Audiometric assessment must be done by a certified audiologist.

7.1.2.7 Functional Assessment of Cancer Therapy-Nasopharyngeal (FACT-NP)

FACT-NP is a fully scalable, cancer-specific Patient Reported Outcome instrument containing 43 items, scored on a range of 0-172. The instrument has been psychometrically validated (Tong 2009) and has been used in Hong Kong to assess concerns specific to the nasopharyngeal cancer population. FACT-NP is available in English, traditional and simplified Chinese versions. FACT-NP is estimated to take approximately 12 minutes.

7.1.2.8 Radiotherapy Simulation

Refer to section 5.2.3.2

7.1.2.9 Acute Radiation Toxicity Scoring

Refer to section 5.2.3.6

7.1.2.10 Dental Clearance

Refer to section 5.2.3.2

7.1.2.11 Late Radiation Toxicity Scoring

Refer to section 7.2.4

7.1.3 Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory

This will be performed in accordance to the flow chart in Section 6.

7.1.4 Tumor Imaging and Assessment of Disease

7.1.4.1 Initial Tumor Imaging

Evaluation of tumor extent is required within 28 days prior to allocation.

For loco-regional staging, contrast enhanced MRI of the nasopharynx and neck is preferred. If MRI is medically contraindicated, contrast enhanced CT scan with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement) may be used.

For distal disease staging, full body FDG PET-CT is preferred. Alternatively, contrast enhanced CT of the chest, abdomen and bone scan may be used.

The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

7.1.4.2 Tumor Imaging During the Study

7.1.4.2.1 Tumor Imaging After Day 1 (before Day 8) of second cycle of induction chemotherapy

Contrast enhanced MRI of the nasopharynx and neck has to be repeated with radiotherapy simulation procedure will have to be repeated after Day 1 (before Day 8) of second cycle of induction chemotherapy. This is to allow adequate time for planning so as not to delay the subsequent concurrent chemo-radiation treatment. Patients undergoing post-induction

treatment planning scans should be immobilized in as similar position as possible with the pre-induction treatment position. If MRI is medically contraindicated, contrast enhanced CT scan with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement) may be used. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.

7.1.4.2.2 Tumor Imaging 3 Months Post Chemo-radiation

This first post treatment scan to assess response should be performed at 12 weeks (+/-7 days) from the end of radiotherapy. Contrast enhanced MRI of the nasopharynx and neck is preferred. If MRI is medically contraindicated, contrast enhanced CT scan with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement) may be used.

7.1.4.2.3 Annual Imaging

This first post treatment annual scan to assess response should be performed at 52 weeks (+/-10 days) from the end of radiotherapy.

For loco-regional staging, contrast enhanced MRI of the nasopharynx and neck is preferred. If MRI is medically contraindicated, contrast enhanced CT scan with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement) may be used.

For distal disease staging, full body FDG PET-CT is preferred. Alternatively, contrast enhanced CT of the chest, abdomen and bone scan may be used.

More frequent imaging may be performed if clinically indicated.

Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 7.1.4.2.6), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.4.2.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 7.1.4.2.6.

7.1.4.2.4 End of Treatment and Follow-up Tumor Imaging

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

7.1.4.2.5 RECIST 1.1 Assessment of Disease

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

7.1.4.2.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

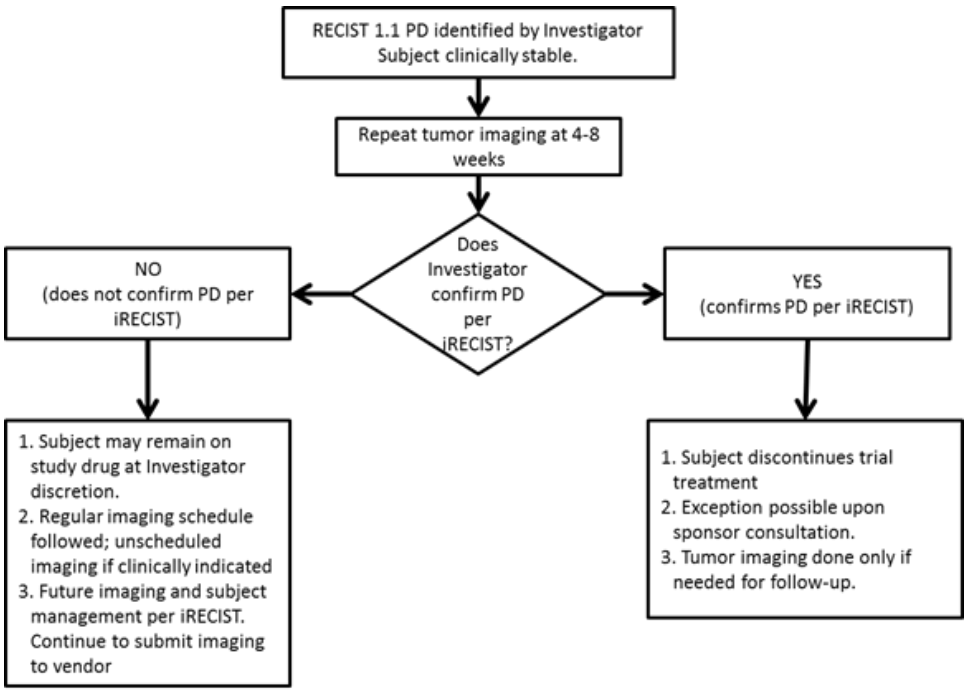
A description of the adaptations and iRECIST process is provided in Appendix 4, with additional detail in the iRECIST publication (38). iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

Table 5 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1..

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



7.1.4.3 Mandatory Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.4.3.1 PD-L1 Status

All subjects should submit either a newly obtained core or excisional biopsy or archival tissue (FNA not adequate for both archival and new tissue samples) to a central lab for characterization of PD-L1 status prior to treatment allocation.

Note: Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide section date , otherwise a new specimen will be requested.

If the sample is determined to be non-evaluable by the central lab, a new sample should be submitted if available. This may include additional cut slides that are outside of the 14 -day window noted above.

Detailed instructions for tissue collection, processing, and shipment are provided in the Operations Manual.

If the subject signs the Future Biomedical Research consent, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research.

7.1.4.3.2 Plasma Epstein - Barr virus DNA (pEBV DNA)

Blood for plasma EBV DNA analysis is to be drawn at baseline before start of any neoadjuvant chemotherapy (B0), then every 3 weeks during neoadjuvant pembrolizumab-cisplatin-gemcitabine chemotherapy (B1 and B2) and concurrent pembrolizumab-cisplatin-radiation (B3 and B4), at 1 week after completion of IMRT (B5), 6-8 weeks post-RT(B6), and every 3 months during maintenance pembrolizumab (B7-10).

- Time point for the blood collection:
    - B0* – Baseline
    - B1 – Cycle 1 Day 1
    - B2 – Cycle 2 Day 1
    - B3* –Week 1 (before RT)
    - B4* – Week 4
    - B5 – 1week post RT
    - B6* – 6-8 weeks post RT
    - B7-B10* – 3, 6, 9 and 12 months post RT (x4)

*Blood for pEBV DNA can be collected in same EDTA tube at time point for both pEBV DNA and ctDNA collection at B0, B3, B4, B6, B7-10 (see 7.1.4.3.3 below).

All samples are to be submitted for central testing. Collection, storage, and shipment instructions for the samples will be provided in the Operations Manual.

If the subject signs the Future Biomedical Research consent, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research.

7.1.4.3.3 Blood for circulating tumor DNA (ctDNA) and peripheral blood mononuclear cells (PBMC) isolation

Blood for ctDNA and PBMC isolation will be collected at baseline before start of any neoadjuvant chemotherapy (B0), before start of RT (week 1; B3) and during RT (week 4; B4), at 6-8 weeks post-RT (B6) and 3, 6, 9 and 12 months post-RT (B7-10).

All samples are to be submitted for central testing. Collection, storage, and shipment instructions for the samples will be provided in the Operations Manual.

If the subject signs the Future Biomedical Research consent, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research.

7.1.4.3.4 Fresh tumor biopsy for molecular studies

Fresh tumor biopsy will be collected at the following time point:

T0 – stands for timepoint 0 and is the baseline tumor biopsy (before C1D1)

T1 – stands for timepoint 1 and is the tumor biopsy after C2D1 neoadjuvant chemo (before RT)

T2 – stands for timepoint 2 and is the tumor biopsy at 6-8 weeks after completion of RT

T3 – stands for timepoint 3 and is the tumor biopsy at any time during or after treatment completion when suspected recurrent or metastatic lesion present

Fresh tumor biopsy will be processed for molecular studies as below:

a) 1 core of tissue: Fixed in Formalin for Paraffin Embedding (FFPE) for immunohistochemistry (IHC) study

b) 1 core of tissue: Fresh in Hypothermosol or frozen in freezing media for single cell RNA sequencing (scRNAseq) study

c) 1 core of tissue: fresh frozen sample for bulk RNA/ TCR sequencing study

All samples are to be submitted for central testing. Collection, storage, and shipment instructions for the samples will be provided in the Operations Manual.

If the subject signs the Future Biomedical Research consent, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research.

7.1.5 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	Free thyroxine (T4)
WBC (total and differential)	Blood Urea Nitrogen or Urea	Specific gravity	Thyroid stimulating hormone (TSH)
Red Blood Cell Count	Calcium	Microscopic exam *(If abnormal results are noted)*	Blood for correlative studies
Absolute Neutrophil Count	Creatinine	Urine pregnancy test †	
Absolute Lymphocyte Count	Glucose		
	Lactate dehydrogenase (LDH)		
Coagulation:* International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	Phosphorus/phosphate		
	Magnesium		
	Potassium		
	Sodium		
	Total Bilirubin		
	Total protein		
	Uric Acid		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
* Only required at main study screening

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.6 Other Procedures

7.1.6.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.6.2 Blinding/Unblinding

[Not applicable]

7.1.7 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.7.1 Screening

7.1.7.1.1 Screening Period

Main study screening period is -28 to -1 day. During the main study screening period, subjects will sign informed consent and receive clinical assessments once meet the inclusion criteria. Please refer to section 6.0 – Trial Flow Chat.

7.1.7.2 Treatment Period

Pembrolizumab in combination with gemcitabine-cisplatin for 2 cycles at week 1&2 and week 4&5 (±3days), then followed by concurrent pembrolizumab-cisplatin-radiation from week 7 to week 14, and then maintenance pembrolizumab monotherapy given every 3 weeks for 12 doses. Please refer to section 6.0 – Trial Flow Chat.

7.1.7.3 Post-Treatment Visits

7.1.7.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.7.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.1.7.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the MSD's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

MSD product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by MSD for human use.

Adverse events may occur during the course of the use of MSD product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

● All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

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

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify MSD.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to MSD

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a MSD product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of MSD's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to MSD Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to MSD

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to MSD Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to MSD

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of MSD's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the MSD in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by MSD for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to MSD Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the MSD product, must be reported within 24 hours to the Sponsor and within 2 working days to MSD Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to MSD product that is brought to the attention of the investigator at

any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to MSD Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the MSD Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the MSD Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to MSD & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to MSD Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to MSD Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to MSD product, must be reported within 2 working days to MSD Global Safety.

Events of clinical interest for this trial include:

1. an overdose of MSD product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of MSD product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a MSD product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to MSD within 2 working days to meet certain local requirements); **or**	

	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to MSD within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause MSD product to be discontinued?	
Relationship to MSD Product	Did MSD product cause the adverse event? The determination of the likelihood that MSD product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between MSD product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely MSD product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to MSD product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of MSD product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to MSD Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was MSD product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to MSD product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MSD PRODUCT, OR IF REEXPOSURE TO MSD PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding MSD product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of MSD product relationship).**
Yes, there is a reasonable possibility of MSD product relationship.		There is evidence of exposure to MSD product. The temporal sequence of the AE onset relative to the administration of MSD product is reasonable. The AE is more likely explained by MSD product than by another cause.

No, there is not a reasonable possibility of MSD product relationship	Participant did not receive the MSD product OR temporal sequence of the AE onset relative to administration of MSD product is not reasonable OR the AE is more likely explained by another cause than the MSD product. (Also entered for a participant with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to the conduct of any analysis, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study (this includes the exploratory analyses for the Optional Sub-Study protocol which will also be documented in a separate sSAP). Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2.

Study Design Overview	A phase 2 study of neoadjuvant pembrolizumab-gemcitabine-cisplatin followed by concurrent pembrolizumab-cisplatin-radiation and then maintenance pembrolizumab in previously untreated stage IVA nasopharyngeal cancer
Treatment Assignment	Open label, single arm, non-randomized
Analysis Populations	Safety: all subjects received at least one dose of pembrolizumab (safety population) Efficacy: intent-to-treat (ITT) in eligible population
Primary Endpoint	-Two-year progression free survival
Key Secondary Endpoints	-Grade 4 mucositis/skin reaction or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to protocol treatment *during* the first year

	-Grade 4 mucositis/skin reaction or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to protocol treatment occurring ***after*** the first year; -Patient tolerability to each component (neoadjuvant, concurrent and maintenance part) of the protocol treatment regimen; -Other ≥ Grade 3 adverse events; -Death during or within 30 days of discontinuation of protocol treatment; -One- and two-year distant metastases rates; -One- and two-year local-regional progression rates; -One- and two-year second primary rates; -One- and two-year overall survival rates.
Independent Review of Adverse Events related to Safety Endpoints	All grade 3/4 mucositis/skin reactions (of any attribution) and all grade 5 adverse events will be assessed by an independent oncologist not associated with this study. The grade and attribution will be reported in two ways: as scored by the treating institution and as scored by the independent reviewer.
Interim Reports to Monitor Study Progress	Interim reports will be prepared twice each year until the final analysis has been completed. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events. This study will be monitored by the Comprehensive Cancer Trials Unit (CCTU) of The Chinese University of Hong Kong. Study data will be submitted in Case Report Form by electronic means to CCTU data manager.

Interim Analysis of Adverse Events	Interim analysis will be conducted after accrual of 14 eligible patients. Patient accrual will be suspended after 14 eligible patients has been entered and the study will not be reopened to accrual until the data for the first evaluation after the concurrent phase have been received for all 14 eligible patients and the rate of adverse events is determined to be acceptable. While the co-primary safety endpoint is the rate of Grade 4 mucositis /skin reaction and any Grade 5 adverse events in the first year, for practical reasons the analysis to evaluate the rates will only require that data for the concurrent phase have been received for all 14 eligible patients. Many patients also will have data by this time of the maintenance phase, and these data will be included. The suspension will be 3-6 months in duration, allowing time for patients to complete the concurrent component and for the data analysis to be performed. Every method should be made to complete the RT delivery to all eligible patients before the interim analysis started. The rates of all Grade 3/4 mucositis/skin reaction or all Grade 5 adverse event by grade and attribution will be reported in two ways: as scored by treating institution and as scored by the independent reviewer. Patients with Grade 4 mucositis/skin reaction or any Grade 5 adverse event as described in section 8.2.1 will be identified. At the interim safety analysis, if there are 3 or more such events out of 14 eligible patients by either institutional scoring or independent review, the study Principle Investigators (PIs) will review the data pertaining to these events. After their review, the PIs and study statistician will make a recommendation to the Trial Steering Committee, and the corporate sponsor for their consideration. These committee and individuals jointly will decide the future course of action for the study, including if a specific treatment component need to be dropped or modified (refer to section 8.2.2, Analysis for Reporting the Initial Treatment Results). If there are 3 or more such events observed prior to the accrual of 14 eligible patients in the first stage before

	formal interim analysis, or 4 or more such events observed prior to the accrual of 42 eligible patients in stage II, confirmed by either institutional scoring or independent review, the study accrual will be suspended immediately. The study PIs will review the data pertaining to these events. After their review, the study PIs and study statistician will make a recommendation to the Trial Steering Committee, and the corporate sponsor for their consideration. These committee and individuals jointly will decide the future course of action for the study, including if a specific treatment component need to be dropped or modified (refer to section 8.2.2, Analysis for Reporting the Initial Treatment Results).
Independent Trial Steering Committee	The Trial Steering Committee is responsible to review the trial progress and safety issues. The committee will be composed of two oncologists and one statistician, who are independent of the clinical trial team.
Sample Size and Power	The total sample size required for the study is 46 patients. (Refer to section 8.2.1)
Statistical Methods for Key Efficacy and Safety Analyses	Refer to section 8.2.2

8.2 Statistical Analysis Plan

8.2.1 Sample Size and Power

Interim analysis for safety endpoints

The baseline rates used in this study are based upon the completed phase II studies of RTOG 0615 bevacizumab-cisplatin-RT (26) and cetuximab-cisplatin-RT (27).

Since there is limited experience with the proposed protocol regimen, the study will determine whether it can be delivered per protocol prescription and is safe. All grade 3/4 mucositis/skin reactions (of any attribution) and all grade 5 adverse events will be assessed by an independent oncologist not associated with this study. An interim safety analysis after accrual of first 14 subjects will be conducted.

There is particular concern with the incidence in NPC patients with increased rate of grade 4 mucositis or skin reaction, which were the dose-limiting toxicity for head and neck radiation and could potentially be aggravated after incorporation of pembrolizumab into standard chemoradiation protocol. Therefore, the incidence of patients with either grade 4 mucositis/skin reaction or any grade 5 adverse event attributed to the protocol treatment will be used to evaluate safety. The incidence of these events will be examined in the first year from the start of treatment and then beyond the first year. The interim safety analysis will examine safety based only upon the *first year* because follow-up for this time period will be complete and the incidence is expected to be lower beyond the first year.

The targeted sample size is based upon the incidence of patients with either grade 4 mucositis/skin reaction or any grade 5 adverse events assessed to be definitely, probably, or possibly related to protocol treatment during the first year. The unacceptable rate for such adverse events is set at ≥ 15% and the acceptable rate at ≤ 5%. Then the statistical hypothesis would be:

H_0: Incidence of patients with either grade 4 mucositis/skin reaction or any grade 5 adverse event for the protocol treatment regimen ≤ 0.05

H_A: Incidence of patients with either grade 4 mucositis/skin reaction or any grade 5 adverse event for the protocol treatment regimen ≥ 0.15

The following table gives the number of patients with the above specified adverse events that are considered unacceptable as calculated by the method of Fleming (39) for a two-stage design where the type I error and the statistical power were set at 0.14 and 0.83, respectively. The first stage will utilize one-third of the required sample size thus permitting an earlier formal evaluation of adverse events.

Number of patients with specified adverse events	**Total number of evaluable patients**
3	14
4	42

The first stage required 14 eligible patients; three or more events would be considered unacceptable. At the second stage, four events in 42 patients were regarded as unacceptable.

To allow for up to 10% of patients later found to be ineligible or not start protocol treatment, four more patients will be entered on the study in addition to the 42 evaluable subjects. Therefore the **total sample size required for the study is 46 patients.** Two of these four

patients will be entered for the first stage of the study, and the remaining two patients will be entered for the second stage.

Patient tolerability also will be evaluated in terms of protocol treatment delivery. The protocol treatment regimen will be considered as 3 treatment components (neoadjuvant, concurrent and maintenance phase) for tolerability assessment. A tolerability rate of 75% will be considered the minimum acceptable rate for a treatment component, while a rate less than 50% will be considered unacceptably low. If the true tolerability rate is 75% or more, there is less than a 1% chance that the regimen will be identified as unacceptable assuming a binomial distribution with a one-sided test. If the true tolerability rate is 50% or less, there is less than a 1% chance that the regimen will be identified as acceptable assuming a binomial distribution with a one-sided test.

Primary efficacy endpoint

Treatment efficacy will be evaluated as the primary efficacy endpoint (2-year progression free survival) and as other secondary endpoints. The rates of local control, distant metastasis, progression free survival, and overall survival in this study will be compared with the historical rates from previous publications. The addition of pembrolizumab is hypothesized to reduce rate of both local recurrence and distant metastases.

According to the data form the Hong Kong NPC study group 0502 trial (Chan AT, Hui EP et al, *JCO 2018 in press*), the progression free survival rate in the total plasma EBV DNA screening population (n=789) by stage (UICC 1997) is as follows:

Overall Stage (UICC 1997)	N	No. of event	No. of event before 2 year	1-yr rate (%)	2-yr rate (%)	3-yr rate (%)	5-yr rate (%)
IIB	222	57	31	91.0	86.0	80.7	76.1
III	381	104	70	88.7	81.5	77.7	72.1
IVA	113	55	35	83.1	68.9	62.0	52.8
IVB	73	36	25	76.5	65.4	54.2	49.8
IVA-IVB (=stage IVA in UICC 2018)	186	91	60	80.5	67.4	59.0	51.4

Based on the historic data, the 2-year progression free survival for UICC 2018 Stage IVA (correspond to stage IVA and IVB in UICC 1997) ranged from 65.4% to 68.9%. We assume that the 2-year progression fee survival will be improved at least from 66.0% to 83.0% (better than Stage III) with the combined chemo-immunotherapy regimen.

Ho: The 2-year rate of progression-free survival should be ≤ 0.66

H1: The 2-year rate of progression-free survival should be ≥ 0.83

By using Fleming one-stage design where type I error and statistical power was set as 0.05 and 0.80, respectively.

Number of patients with events within 2 years	Total number of evaluable patients
10	42

The number of evaluable patients required is 42. If 10 or more patients developed events (progression or death) within 2 years, this would be considered unacceptable. If less than 9 patients had the events, we can then reject Ho and conclude that the combined treatment is effective.

8.2.2 Statistical Methods

The rates of tolerability and adverse events will be estimated using a binomial distribution along with their associated 95% confidence intervals. Only adverse events assessed by the treating institution as definitely, probably, or possibly related to protocol treatment will be considered in evaluating the primary endpoint. Rates of distant metastases, local-regional progression, and second primary tumors will be estimated using the cumulative incidence method while progression-free and overall survival rates will be estimated using the Kaplan-Meier method. Only the first event will be considered when evaluating efficacy endpoints other than overall survival. All failure times will be measured from the date of registration. The following table shows how each first event would be counted for local-regional progression, distant metastases, second primary tumors, and progression-free survival.

First Event	Additional Information Needed	Local-Regional Progression	Distant Metastases	Second Primary Tumors	Progression-Free Survival
None		Censored	Censored	Censored	Censored
Local-Regional progression		Failure	Competing risk	Competing risk	Failure
Distant metastasis		Competing risk	Failure	Competing risk	Failure
Second primary tumor		Competing risk	Competing risk	Failure	Censored
Death	COD=study cancer	Failure	Competing risk	Competing risk	Failure
Death	COD=SPT	Competing risk	Competing risk	Failure	Failure
Death	COD=protocol treatment	Competing risk	Competing risk	Competing risk	Failure
Death	COD=other cause	Competing risk	Competing risk	Competing risk	Failure

Death	COD=unknown	Failure	Competing risk	Competing risk	Failure
Non-protocol radiation therapy		Failure	Competing risk	Competing risk	Failure
Non-protocol chemotherapy (or biologic)		Failure	Competing risk	Competing risk	Failure
Surgery of primary	Pathology=tumor	Failure	Competing risk	Competing risk	Failure
Surgery of primary	Pathology=no tumor	Non-event, continue	Non-event, continue	Non-event, continue	Non-event, continue
Surgery of primary	Pathology=unknown	Failure	Competing risk	Competing risk	Failure
Surgery of nodes	≤ 15 weeks from RT end	Non-event, continue	Non-event, continue	Non-event, continue	Non-event, continue
Surgery of nodes	> 15 weeks from RT end; pathology=tumor	Failure	Competing risk	Competing risk	Failure
Surgery of nodes	> 15 weeks from RT end; pathology=no tumor	Non-event, continue	Non-event, continue	Non-event, continue	Non-event, continue
Surgery of nodes	> 15 weeks from RT end; pathology=unknown	Failure	Competing risk	Competing risk	Failure

COD = cause of death

Analysis for Reporting the Initial Treatment Results

The analysis to report the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. Only eligible patients with both on-study and follow-up information that has started protocol treatment will be included. The emphasis of this analysis will be on treatment compliance and adverse events. The usual components of this analysis are:

- Tabulation of all cases entered, and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Compliance rate for treatment delivery with respect to the protocol prescription;
- Observed results with respect to the study endpoints described in section 8.1.

The rates of adverse events and tolerability will be estimated along with their associated 95% confidence intervals. Patients with Grade 4 mucositis/skin reaction or any Grade 5 adverse event as described in Section 8.2.1 will be identified. If there are 4 or more such patients out of the first 42 eligible patients by either institutional scoring or independent review, the protocol treatment will be considered to have an unacceptably high adverse event rate to use this treatment without modification in subsequent follow-up phase III trial. In addition, the

tolerability rate for each treatment component (neoadjuvant, concurrent and maintenance phase) will be computed. If the percentage is less than 50% for a component, then that component will be considered to have an unacceptably low tolerability rate to use without modification in the follow-up phase III trial, then the treatment component will be dropped or modified.

Analysis for Reporting the Final Treatment Results

The analysis to report the final results of treatment will be undertaken when each patient has been potentially followed for a minimum of 2 years. Only eligible patients with both on-study and follow-up information that started protocol treatment will be included. The emphasis of this analysis will be on local-regional progression and distant metastases. The usual components of this analysis are:

- Tabulation of all cases entered, and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Compliance rate for treatment delivery with respect to the protocol prescription;
- Observed results with respect to the endpoints described in Section 8.1.

The rates of local-regional progression, distant metastases, second primary tumors, progression-free survival, and overall survival at one and two years will be estimated along with their associated 95% confidence intervals. These rates also will be compared with historical rates from previous publications.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by MSD as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

All commercially available products not included in Table 8 (e.g. gemcitabine, cisplatin, and other supportive medications) will be provided by hospital pharmacy at study site as per local guideline.

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from MSD or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and

institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor. By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.2 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in Section 12.1 - MSD Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents. The investigator shall prepare and maintain

complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents sh all be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files. ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

10.3 Declaration of Helsinki

We abide to the declaration of Helsinki.

10.4 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.5 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.
Detailed information regarding Data Management procedures for this protocol will be provided separately.

11.0 REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28:4531-8.
2. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol. 2005;23:2346-57.
3. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med. 2008;358:2698-703.
4. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2005;23:515-48.
5. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A. 2001;98:13866-71.
6. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20:337-47.

7. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol. 2004;173:945-54.
8. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.
9. Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009;229:114-25.
10. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol. 2005;25:9543-53.
11. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219-42.
12. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.
13. Pan JJ, Ng WT, Zong JF, Lee SW, Choi HC, Chan LL, et al. Prognostic nomogram for refining the prognostication of the proposed 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer. 2016;122:3307-15.
14. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol. 2016;17:1509-20.
15. Cao SM, Yang Q, Guo L, Mai HQ, Mo HY, Cao KJ, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase III multicentre randomised controlled trial. Eur J Cancer. 2017;75:14-23.
16. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2016;388:1883-92.
17. Hsu C, Lee SH, Ejadi S, Even C, Cohen RB, Le Tourneau C, et al. Safety and Antitumor Activity of Pembrolizumab in Patients With Programmed Death-Ligand 1-Positive Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Study. J Clin Oncol. 2017;35:4050-6.
18. Weiss GJ, Waypa J, Blaydorn L, Coats J, McGahey K, Sangal A, et al. A phase Ib study of pembrolizumab plus chemotherapy in patients with advanced cancer (PembroPlus). Br J Cancer. 2017;117:33-40.
19. Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, Borghaei H, Gettinger S, et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34:2969-79.
20. Sanborn RE, Duffy RM, Fisher BK, Perlewitz KS, Redmond WL, Kpguchi Y. A phase I/II study of pembrolizumab (P) with gemcitabine (G) in patients (Pts) with previously-treated

advanced non-small cell lung cancer (NSCLC): Phase I safety results. DOI: 101200/JCO20173515_supple20605, Journal of Clinical Oncology 35, no 15_suppl. 2017.
21. Primo L, Beckett L, Li Y, Parikh M, Robles D, Aujla P. Combination checkpoint immunotherapy and cytotoxic chemotherapy: Pembrolizumab (Pembro) plus either docetaxel or gemcitabine in patients with advanced or metastatic urothelial cancer. DOI: 101200/JCO2017356_suppl 398 Journal of Clinical Oncology 35, no 6_suppl (February 2017) 398-398. 2017.
22. Wainberg et al. KEYNOTE-059: Efficacy and Safety of Pembrolizumab (pembro) Alone or in Combination with Chemotherapy (chemo) in Patients (pts) With Advanced Gastric or Gastroesophageal (G/GEJ) Cancer. Oral Presentation: ESMO 2017: 8-12 September 2017 in Madrid, Spain.
23. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17:1497-508.
24. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378:2078-92.
25. Powell SF, Gitau MM, Sumey CJ, Reynolds J, Terrell AM, Lohr MM, et al. Safety of Pembrolizumab with Chemoradiation (CRT) in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LASCCHN). Presented at: 2017 ASCO Annual Meeting, June 2-6, 2017; Chicago, Illinois 2017.
26. Lee NY, Zhang Q, Pfister DG, Kim J, Garden AS, Mechalakos J, et al. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol. 2012;13:172-80.
27. Ma BB, Kam MK, Leung SF, Hui EP, King AD, Chan SL, et al. A phase II study of concurrent cetuximab-cisplatin and intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma. Ann Oncol. 2012;23:1287-92.
28. Chow LQM, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol. 2016;34:3838-45.
29. Ma BBY, Lim WT, Goh BC, Hui EP, Lo KW, Pettinger A, et al. Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). J Clin Oncol. 2018:JCO2017770388.
30. Lo YM, Chan LY, Lo KW, Leung SF, Zhang J, Chan AT, et al. Quantitative analysis of cell-free Epstein-Barr virus DNA in plasma of patients with nasopharyngeal carcinoma. Cancer Res. 1999;59:1188-91.
31. Lo YM, Chan AT, Chan LY, Leung SF, Lam CW, Huang DP, et al. Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein-Barr virus DNA. Cancer Res. 2000;60:6878-81.

32. Kim KY, Le QT, Yom SS, Ng RHW, Chan KCA, Bratman SV, et al. Clinical Utility of Epstein-Barr Virus DNA Testing in the Treatment of Nasopharyngeal Carcinoma Patients. Int J Radiat Oncol Biol Phys. 2017;98:996-1001.
33. Chan AT, Lo YM, Zee B, Chan LY, Ma BB, Leung SF, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. J Natl Cancer Inst. 2002;94:1614-9.
34. Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med. 2004;350:2461-70.
35. Chan AT, Ma BB, Lo YM, Leung SF, Kwan WH, Hui EP, et al. Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr virus DNA. J Clin Oncol. 2004;22:3053-60.
36. Brouwer CL, Steenbakkers RJ, Bourhis J, Budach W, Grau C, Gregoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol. 2015;117:83-90.
37. Sun Y, Yu XL, Luo W, Lee AW, Wee JT, Lee N, et al. Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy. Radiother Oncol. 2014;110:390-7.
38. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:e143-e52.
39. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics. 1982;38:143-51.

12.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

◯ Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10 during the protocol-defined time frame in Section 5.1.1.

Table 10 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The

reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). *Delete footnote "b" for all trials evaluating pembrolizumab as monotherapy. Include for all trials evaluating pembrolizumab as a combination therapy.* b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, after the last dose of study treatment, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

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

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (38).

Appendix 5: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.4.4 – Future Biomedical Research 7.1.4.4 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by study Principle Investigator (PI) focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by PI or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the central encrypted database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately- consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the institutional approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (Section 8.0 – Statistical Analysis Plan). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The

clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the institution has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de- identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the designated facility to a central encrypted database. The second code will be logged into the primary biorepository database and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the central encrypted database under strict security policies and procedures. The encrypted database will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated

conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by PI, or an additional third party (e.g., a university investigator) designated by PI. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the PI from the encrypted database. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to PI.

6. Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact PI and a form will be provided by PI to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from PI to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be

destroyed according to institutional policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by PI. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards to protect against unauthorized access. The encrypted database maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub- trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by PI on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, PI will publish the results without revealing specific subject information, inform all trial sites who participated in the clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

11. Risks versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The PI's institution has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

13. Questions

Any questions related to the future biomedical research should be directly to study PI.

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15;

http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html