TITLE: Immuno-Chemotherapy as single treatment modality for Larynx Preservation (ICoLP)

PI: Renata Ferrarotto, MD (Head and Neck Medical Oncology)

Co-PIs:
Ed Diaz Jr, MD (Head and Neck Surgery)

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1.0 TRIAL SUMMARY

Abbreviated Title	ICoLP
Trial Phase	II
Clinical Indication	Larynx squamous cell carcinoma (LSCC)
Trial Type	Single arm
Type of control	NA
Route of administration	Intravenously
Trial Blinding	NA
Treatment Groups	One
Number of trial participants	Up to 25
Estimated enrollment period	24 months
Estimated duration of trial	36 months
Duration of Participation	Patients will be followed for 1 year
Estimated average length of treatment per patient	18 weeks

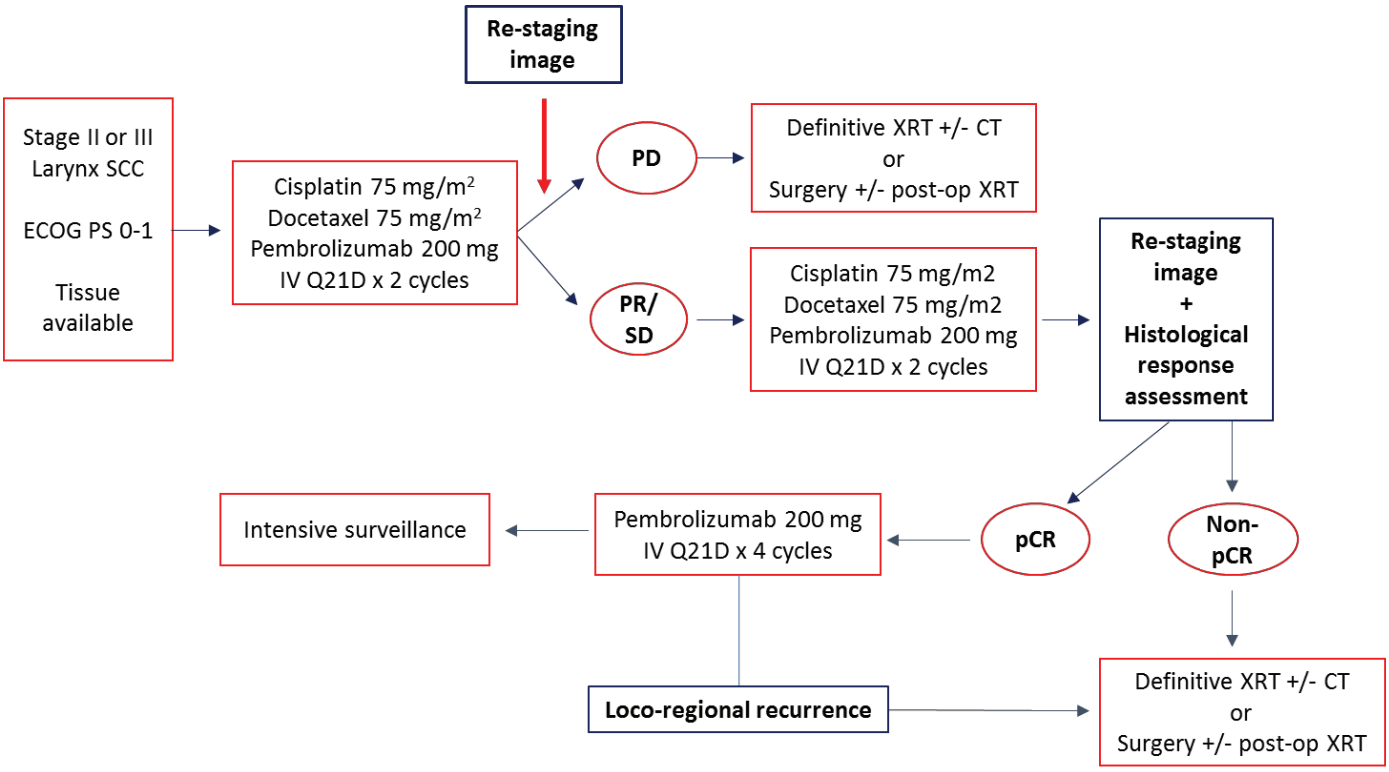
2.1 TRIAL DESIGN

2.2 Trial Design

This is a single arm phase II study that will evaluate the combination of pembrolizumab, cisplatin, and docetaxel (PCD) as single treatment modality in patients with stage II or III larynx SCC.

2.3 Trial Diagram

Figure 1. Study Design.



Cancer stage as per TNM 8th edition [see appendix 10.5]; ECOG PS: ECOG performance status [see appendix 10.1]; PD: progression of disease; PR: partial response; SD: stable disease; XRT: radiotherapy, CT: chemotherapy; Q21D: each 21 days; post-op: post-operative; pCR: pathologic complete response, Definitive: Standard of care.

3.1 OBJECTIVE(S) & HYPOTHESIS(ES)

3.2 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the clinical benefit rate (CBR) of patients with stage II or III larynx squamous cell carcinoma (SCC) after 2 cycles of pembrolizumab, cisplatin and docetaxel (PCD), and the pathologic complete response (pCR) rate after 4 cycles of PCD.

Hypothesis: In patients with stage II or III larynx SCC, PCD will lead to CBR in the vast majority of patients. Furthermore, PCD will lead to durable pCR in a subset of patients.

3.3 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine safety and tolerability of PCD in patients with larynx SCC.

Hypothesis: PCD will have the toxicity profile expected for each agent alone, without significant overlapping toxicity.

(2) **Objective**: To determine the laryngeal preservation rate (LPR) at 2 years in the overall population and in the subgroup who achieves a pCR.

Hypothesis: PCD in the induction setting or as single treatment modality will lead to a rate of laryngeal preservation at 2 years that is comparable or higher to historical controls.

(3) **Objective:** To determine the 2 year relapse-free survival (RFS) and overall survival (OS) in the overall population and in the subgroup who achieves a pCR.

Hypothesis: Laryngeal SCC patients treated with PCD will have favorable relapse-free survival and overall survival outcomes when compared to historical controls.

(4) **Objectives:** To determine patient-reported outcomes (PROs) using M.D. Anderson Symptom Inventory-Head and NECK (MDASI-HN) and swallow function using Dynamic Imaging Grade of Swallowing Toxicity (DIGEST).

Hypothesis: PCD as single treatment modality will lead to significantly better PROs and improved swallow and speech functions as compared to patients treated with multi-modality therapy.

3.4 Exploratory Objective

(1) **Objective:** To assess predictive tissue and blood-based biomarkers of benefit from PCD in larynx SCC.

Hypothesis: Analysis of tissue and blood biomarkers before and after treatment may identify predictive markers of benefit from PCD and will increase the understanding of the immune biology of locally advanced larynx SCC.

4.1 BACKGROUND & RATIONALE

4.2 Background

The larynx performs three vital functions: maintenance of airway patency, occlusion of the airway during the pharyngeal phase of swallowing, and voice production. Optimal treatment maximizes these functional outcomes (ie, voice quality, swallowing ability) and survival.

In spite of total laryngectomy be an effective treatment for larynx squamous cell carcinoma, loss of the natural voice and the stigma, life style, and voice restrictions of a permanent stoma significantly impair quality of life, frequently leads to social isolation, and depression [1].

Both, radiation therapy (RT) and laryngeal preservation surgery can cure a high proportion of patients with early stage disease (Stage I and II). RT is often preferred because functional outcomes, particularly voice quality, are perceived to be better. Selected patients with T2 cancers (eg, bulky, invasive T2 cancers with impaired cord mobility or subglottic extension) are appropriate for concurrent chemoradiation due to worse local control with radiotherapy alone [2-5].

Patients with early stage laryngeal cancer are less likely to have prolonged acute and long-term permanent toxicity than patients with advanced laryngeal SCC who require larger RT fields and concurrent chemotherapy[6], however, prolonged larynx edema, chondritis, laryngeal and pharyngeal stenosis can occasionally occur in patients with early stage disease treated with single modality RT [7,8].

For patients with locally advanced disease (stage III or IV), concomitant chemoradiation or induction chemotherapy followed by RT are acceptable standard of care treatment options as an organ preservation approach; however, radiotherapy with or without chemotherapy can lead to significant long-term morbidity and a minority of patients will have a functional anatomic preserved organ [9,10].

Long-term results from RTOG 91-11, which included 64% of stage III patients, demonstrated improved long-term survival with induction chemotherapy followed by RT, likely due to long-term side effects attributed to concurrent chemoradiation (such as recurrent aspiration, stroke, etc..) not captured on the study [11,12]. At one year, 23% of patients who received concurrent chemoradiation could only swallow liquid or soft foods, and 3% could not swallow at all. In the radiotherapy single modality, 15% were limited to soft food or liquids and 3% could not swallow. The subgroup who received sequential therapy had only 9% of patients limited to soft or liquid food. The 2 year disease-free interval and overall survival was approximately 55% and 75% respectively for all groups. Systemic therapy (Cisplatin and 5-Fluouracil) in the induction setting reduced the rate of distant metastasis.

Other studies have confirmed that induction chemotherapy decreases distant metastasis in patients with locally-advanced HNSCC, and there is a benefit in overall response rate and survival of using three (Cisplatin, Docetaxel, and 5-Fluouracil or TPF) versus two (Cisplatin and 5-Fluourocil or PF) chemotherapy agents [13,14]. TPF in larynx SCC leads to an overall response rate of 85%[15]; however, toxicity limits the use of triple agent chemotherapy in a significant proportion of patients.

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. Keytruda® (pembrolizumab) 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. It has been FDA approved for the treatment of recurrent or metastatic head and neck SCC [16] given its encouraging activity in this patient population. Exploratory analysis of prospective clinical trials suggest that clinical benefit of single agent pembrolizumab is higher when PD-L1 is expressed in at least 1% of the tumor cells and/or in lymphocytes and macrophages in the tumor microenviroment, which occurs in approximately 78% of head and neck squamous cell carcinoma [PMID: 27718784, 30509740, 27646946].For more details on specific indications refer to the Investigator brochure.

In metastatic non-small cell lung cancer (NSCLC), pembrolizumab combined with platinum-doublet chemotherapy has improved overall response rates and overall survival in two randomized phase III trials when compared to chemotherapy alone without a significant increase in toxicity and irrespective of PD- L1 status. Dexamethasone as pre-medication was used as per standard guidelines and did not seem to impact the benefit of pembrolizumab added to chemotherapy. Pembrolizumab combined to platinum and pemetrexed or platinum and paclitaxel/nab-paclitaxel are currently standard of care first line systemic therapy in NSCLC [PMID: 30429032, 30280635, 29658856].

Considering the encouraging activity and safety profile seen with carboplatin, paclitaxel and pembrolizumab in metastatic non-small cell lung cancer; that most benefit from TPF in head and neck SCC is thought to be derived from cisplatin and docetaxel; and that 5-FU requires continuous infusion and has diarrhea as a common adverse event, we believe that pembrolizumab combined with cisplatin and docetaxel will be well tolerated and have significant activity in patients with stage II or III larynx SCC. Furthermore, we hypothesize that a proportion of patients treated with this regimen will achieve a durable pathologic complete response and will be cured with single modality systemic therapy.

4.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades[18]. 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 [19,20].

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) [21,22].

The structure of murine PD-1 has been resolved [23]. 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 [22,24-26]. 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 [27,28]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in larynx squamous cell carcinoma.

4.2.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Our group has demonstrated in a single arm phase II study that 33% of patients with T2-4, N0-1 larynx SCC treated with TIP (paclitaxel, ifosfamide, cisplatin) achieved a complete pathologic response (pCR) with durable remission and no evidence of disease recurrence at 5 years [29]. A 10-year update of this study revealed that none of the patients who achieved a pCR and were disease-free at 5 years recurred (unpublished data, manuscript in preparation), suggesting that a subset of larynx SCC can be cured with systemic therapy alone. The functional outcomes of patients who received systemic therapy as a single treatment modality were remarkable with normal speech and swallow functions.

Larynx SCC is a tobacco-induce neoplasm with a high mutation-burden, which usually correlates with response to pembrolizumab. It is overall a chemotherapy-sensitive disease, however, responses are in general short-lived. Chemotherapy can lead to immunogenic cell death and can augment tumor immunity. PD-1 inhibitors can lead to expansion of intratumoral memory T cells, which can lead to durable responses [30]. Based on the encouraging results reported in the Keynote-021 trial with platinum doublet combined with pembrolizumab, as discussed in Section 4.1 [17], we propose cisplatin, docetaxel, and pembrolizumab will be safe and effective in patients with stage II or III larynx SCC and will lead to cure as a single treatment modality in a subset of patients.

4.2.2 Justification for Dose

4.2.2.1 Chemotherapy

The standard dose of Cisplatin and Docetaxel used in head and neck squamous cell carcinoma is 75 mg/m^2 for both agents administered intravenously over one hour each Q3W [13,15]. Body surface area (BSA) for chemotherapy dose calculation will be determined according to the following formula: BSA (m^2) = [height (cm) x weight (Kg) / 3600].

The actual body weight will be used for BSA calculation, but the investigators will consider adjusted or ideal body weight if the BSA exceeds 2.0 m$^{2.}$ BSA should be recalculate prior to the start of every cycle of therapy.

For patients with contra-indication to cisplatin, carboplatin AUC 6 using the Calvert method can

be used.

Carboplatin dose (mg) = AUC x [GFR (ml/min) + 25 (ml/min)].

4.2.2.2 Pembrolizumab

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 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Pathologic complete response has predicted improved long-term outcomes in many neoadjuvant trials in breast cancer [31]. Concomitant systemic therapy and radiation therapy for organ preservation is a standard of care treatment for larynx SCC[11] and has recently become an accepted treatment modality in rectal cancer, sparing unnecessary morbidity, mortality, and functional consequences associated with radical surgery without loss of oncological safety [32,33].

Larynx SCC is an overall chemo – and radio- sensitive tumor. There is evidence that when pathologic complete response is achieved in larynx SCC, irrespective of its means (if by systemic therapy as single modality or by concurrent radiotherapy), a proportion of patients will be cured[29]. Sparing radiation therapy or surgery can significantly improve the function of the preserved organ and maintain patient's quality of life, therefore, patient reported-outcomes is a secondary endpoint and will be assessed longitudinally with validated tools (MDASI-HN and DIGEST). Importantly, if patients recur, particularly in the context of close follow-up, they are highly salvageable with total laryngectomy or radiotherapy plus or minus chemotherapy.

Since the higher risk of recurrence are within the first 2 years following definitive treatment, and in order to compare our results with the available literature, our secondary endpoints include laryngeal preservation rate, relapse-free survival, and overall survival at 2 years.

4.2.3.2 Biomarker Research

There is substantial interest in identifying biomarkers predictive of response to immune checkpoint inhibitors plus or minus chemotherapy in invasive solid tumors. As such, the biomarkers to be evaluated on this study aim at:

(1) identifying the population more likely to benefit from pembrolizumab, cisplatin and docetaxel,

(2) characterizing the immune response before and after treatment,

(3) evaluating the interplay between the immune system, genetic, epigenetic, transcriptomic and phenotypic changes before and after treatment with pembrolizumab, cisplatin, and docetaxel.

Because the biomarker research embedded in this protocol is exploratory, a broad panel of markers will be studied utilizing the most updated knowledge from other clinical and pre-clinical studies related to immune checkpoint blockade at the time of the analysis.

5.1 METHODOLOGY

5.2 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 newly diagnosed, previously untreated, histologically confirmed stage II to III larynx squamous cell carcinoma will be enrolled in this study.

Male participants:

2. A male participant must agree to use a contraception as detailed in Section 10.3 . of this protocol during the treatment period and for at least 150 days after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

3. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Section 10.3 of this protocol
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Section 10.3 during the treatment period and for at least 150 days after the last dose of study treatment.

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

5. Have measurable disease based on RECIST 1.1.

6. Have provided archival tumor tissue sample (minimum of 20 unstained slides) 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.

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

8. 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 or ≥5.6 mmol/L[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 ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
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 institutional standard.

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 treatment (see Section 10.3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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 prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to study treatment.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

4. 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.

5. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

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, with the exception of dexamethasone, that can be given the day prior (D0) until 4 days after chemotherapy (D4) up to 16 mg per day for prevention of chemotherapy-induced nausea, fluid retention, and/or allergic reaction.

7. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal or squamous cell carcinoma of the skin, transitional cell carcinoma of urothelial cancer, carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy, and prostate cancer patients in active surveillance are not excluded.

8. 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.

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

10. Has an active infection requiring intravenous antibiotic therapy.

11. Has a known history of Human Immunodeficiency Virus (HIV).

12. 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 < 615 IU/L) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

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

14. 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.

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

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 150 days after the last dose of trial treatment.

17. as had a solid organ transplant and/or allogenic bone marrow transplant.

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, dysphagia, nausea or vomiting.

5.1.3.2 Contraception

Pembrolizumab and chemotherapy may have adverse effects on a fetus in utero. Refer to Section 10.3 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. 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 Merck 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 Merck. 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 Merck 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

The systemic therapy treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose	Frequency	Route	Treatment Period	Use
*Cisplatin	75 mg/m^2	Q3W	IV	D1 of each 3W cycle, up to 4 cycles	Standard
*Docetaxel	75mg/m^2	Q3W	IV	D1 of each 3W cycle, up to 4 cycles	Standard
Pembrolizumab	200 mg	Q3W	IV	D1 of each 3W cycle, up to 8 cycles	Experimental
**Carboplatin	AUC 6	Q3W	IV	D1 of each 3W cycle, up to 4 cycles	** Standard

* The use of Cisplatin and Docetaxel is standard of care in the induction setting for the patient population being studied, however, the combination of these two chemotherapy agents with pembrolizumab is experimental

** Carboplatin will only be used instead of cisplatin if the study subject has any contra-indication to cisplatin or develop a significant adverse-event during treatment attributable to cisplatin (Eg: nausea and vomiting, increase in serum creatinine)

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). Pembrolizumab will be

administered first, followed by docetaxel and then cisplatin. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis. MDACC will use its own commercial supply of chemotherapy in this study. Pembrolizumab will be provided at no cost to the patient by Merck.

5.2.1.1 Description, Handling and Administration of Docetaxel

Docetaxel will be prepared and administered according to local practice and in accordance with the most recent Package Insert/Data Sheets.

Dexamethasone will not be given prophylactic on Day 0 for fluid retention prior to cycle 1, however, it can be added as a prophylactic medication (up to 16 mg per day the day before and the day after administration) in case severe fluid retention is observed after cycle 1.

5.2.1.2 Description, Handling and Administration of Cisplatin or Carboplatin

Cisplatin or Carboplatin will be prepared and administered according to local practice and in accordance with the most recent Package Insert/Data Sheets.

Pre-medication for Cisplatin: All patients will receive intravenously anti-emetics and appropriate hydration prior to and after cisplatin administration according to current institutional guidelines. Anti-emetics include dexamethasone 12 mg, fosaprepitant 150 mg, and ondensantron 8 mg.

Patients will be counseled to take dexamethasone 4 mg per oral bid and ondansentron 8 mg tid for 2 to 3 days after chemotherapy (D2-D4).

5.2.1.3 Description, Handling and Administration of Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Site 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).

5.2.2 Dose Modification and toxicity management

Toxicities will be graded by using the NCI CTCAE version 5. Refer to the following website for the CTCAE manual or the CTCAE document: **http://ctep.cancer.gov**

5.2.2.1 Definition of Dose Limiting Toxicity

A dose limiting toxicity (DLT) will be defined as Grade 4 neutropenia lasting ≥ 7 days, Grade 3 or 4 febrile neutropenia, Grade 4 anemia, Grade 4 thrombocytopenia or any non-hematologic

toxicity Grade 3 or greater that per Principal Investigator judgement is clinically significant and either possibly, probably or definitely attributable to study therapy. Exceptions include grade 3 infusion reactions that resolve within 24 hours, grade 3 diarrhea, nausea, and/or vomiting that responds to standard medical treatment within 48 hours, grade 3 electrolyte disturbances that respond to correction within 24 hours), and grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic.

5.2.2.2 Dose Modification and toxicity management for docetaxel and cisplatin or carboplatin

The dose modifications outlined below are considered general guidelines. The investigator should use his or her best judgment when determining treatment interruptions and dose modifications. For example, some grade 2 non-hematologic toxicities may require treatment delays and/or dose reductions, and some grade 3 or 4 organ toxicities (e.g., hepatic, renal, cardiac, central nervous system) may require a permanent treatment discontinuation. If one chemotherapy agent (docetaxel or cisplatin/carboplatin) needs to be discontinued, the other chemotherapy agent (cisplatin/carboplatin or docetaxel) may be continued. Docetaxel or cisplatin/carboplatin dose will not be re-escalated once it has been reduced for toxicity.
Prior to receiving any dose of docetaxel and cisplatin / carboplatin, patients must have an ANC $\geq 1.5 \times 10^9$/L and a platelet count $\geq 100 \times 10^9$/L. If the ANC is $< 1.5 \times 10^9$/L and platelet count is $< 100 \times 10^9$/L, the treatment should be delayed for ≤ 3 weeks. If the patient is unable to be treated after a 3-week delay, the patient will be discontinued from chemotherapy. Patients who have discontinued chemotherapy will be allowed to continue on pembrolizumab.

5.2.2.1.1 Dose Modifications for Docetaxel
The dose of docetaxel will be reduced according to the following guidelines.

Thrombocytopenia
- If grade 4 thrombocytopenia occurs, the dose of docetaxel will be reduced by 25% for subsequent cycles. If grade 4 thrombocytopenia persists despite dose reduction, docetaxel treatment will be discontinued.

Neutropenia
The dose of docetaxel will be reduced for the following neutropenic conditions as outlined in **Table 3:**
- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 febrile neutropenia

Table 3: Docetaxel Dose Modifications for Neutropenia

Dose Description	Docetaxel Dose (mg/m^2)
starting dose	75 mg/m^2

1st dose reduction due to neutropenia (patients not receiving prophylactic growth factor support)	75 mg/m^2 add growth factor support
1st dose reduction due to neutropenia (patients receiving prophylactic growth factor support)	65 mg/m^2 continue growth factor support
2nd dose reduction due to neutropenia	50 mg/m^2 continue growth factor support

If grade 4 neutropenia or grade 3-4 febrile neutropenia persists despite dose reduction to 50 mg/m^2 with growth factor support, docetaxel treatment will be discontinued.

Hepatic Dysfunction
The dose of docetaxel will be reduced for abnormal liver function test as outlined in **Table 4**:

Table 4: Docetaxel Dose Modifications for Abnormal Liver Function

Direct Bilirubin		Alkaline Phosphatase		SGOT or SGPT	Action
> ULN	**OR**	> 5 x ULN	**OR**	> 5 x ULN	Delay treatment ≤ 3 weeks until recovery. If recovered*, reduce docetaxel dose by 25%. If not recovered in ≤ 3 weeks, discontinue docetaxel.
≤ ULN	**AND**	≤ 5 x ULN	**AND**	1.6 – 5 x ULN	Reduce docetaxel dose by 25%

*Direct bilirubin ≤ ULN ***and*** alkaline phosphatase ≤ 5 x ULN ***and*** SGOT or SGPT ≤ 5 x ULN

Note: a maximum of two dose reductions per patient are allowed. If liver toxicities persist despite two dose reductions, docetaxel treatment will be discontinued.

Stomatitis

- If grade 3 or 4 stomatitis occurs, the dose of docetaxel will be reduced 25% for subsequent cycles. If grade 3 or 4 stomatitis persists despite dose reduction, docetaxel treatment will be discontinued.

Peripheral Neuropathy

- If grade 3, or clinically significant grade 2 (as judged by the investigator) neuropathy occurs, the dose of docetaxel will be reduced by 25%. If grade 3, or clinically significant grade 2 (as judged by the investigator) neuropathy persists despite two dose reductions, docetaxel treatment will be discontinued.

- If grade 4 neuropathy occurs, docetaxel treatment will be discontinued.

Hypersensitivity Reactions

- There are no dose reductions for hypersensitivity reactions. Management of acute hypersensitivity reaction should follow the Institutional guidelines. Re-treatment with docetaxel will be allowed at the investigator's discretion.
- If grade 4 hypersensitivity reactions occur, docetaxel treatment will be discontinued.

Fluid Retention

- There are no dose reductions for fluid retention.

Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. 2 pound weight gain), prophylactic dexamethasone on the day prior to chemotherapy will be added on the subsequent cycle and patients will be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Taxotere are listed below.

- Triamterene/hydrochlorothiazide one capsule (37.5 mg / 25 mg) po qd up to tid.
- Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

Other Non-Hematologic Toxicities

- If grade 3 or 4 clinically significant (as judged by the treating physician) non-hematologic toxicities occur (other than those listed above), docetaxel treatment will be withheld until the toxicity has resolved to ≤ grade 1 and then reinstituted (if medically appropriate) at a 25% dose reduction. If a grade 3 or 4 clinically significant toxicity

recurs despite two dose reductions, docetaxel treatment will be discontinued.

- If treatment is withheld for > 3 weeks due to a grade 3 or 4 toxicity, docetaxel treatment will be discontinued.

5.2.2.1.2 Modifications for Cisplatin or Carboplatin

If any grade 3 or 4 toxicity occurs that is consistent with the cisplatin or carboplatin side effect profile (e.g., renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range [4000 to 8000 Hz], nausea and vomiting, hyperuricemia, mild to moderate anemia, and irreversible peripheral neuropathy), the dose of cisplatin or carboplatin will be reduced as outlined in **Table 5**. Additionally, the investigator may choose to switch from cisplatin to carboplatin (or vice versa) during cycles 2 to 4 as an attempt to minimize the incidence or severity of platinum-related toxicities.

Table 5: Cisplatin/Carboplatin Dose Modifications

Dose Level	Cisplatin Dose (mg/m^2)	Carboplatin Dose (AUC)
0 Starting Dose	75 mg/m^2	6
-1	60 mg/m^2	5
-2	50 mg/m^2	4

If toxicities persist despite two dose reductions, cisplatin or carboplatin treatment will be discontinued.

5.2.2.2 Dose Modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

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 6.

Table 6 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 (CTCAEv5)**	**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
	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	• Add prophylactic antibiotics for opportunistic infections • 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). • 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
	Grade 4	Permanently discontinue		

				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.
	Grade 2	Withhold		• Monitor changes of renal function

Nephritis and Renal dysfunction	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	
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 7.

Table 7: 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 Antihistamine s 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 _____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)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamine s NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

Grade 4: Life-threatening; pressor or ventilatory support indicated	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.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5 (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. The reason for interruption should be documented in the patient's study record.

5.3 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.

5.3.1 Acceptable Concomitant Medications

Concomitant medication will only be recorded in the medical record.

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.

5.3.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- 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 prophylactic dexamethasone for chemotherapy induced nausea, vomiting, and/or edema, or to modulate symptoms from an event of clinical interest of suspected immunologic etiology.

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.

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

5.4 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 6]. 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 7] 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.

5.5 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 if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment for the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Initiation of any new anticancer therapy not specified in this protocol
- 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, 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

5.6 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

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 STUDY FLOW CHART

Trial Period:	**Screening Phase**	**Treatment**								**Post-Treatment**	
Treatment Cycle/Title:		1	2	3	4	5[a]	6[a]	7[a]	8[a]	Follow Up Visits[b]	
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	3 weeks (± 1 week) after last cycle of treatment	Every 6-12 weeks (± 1 week) up to 2 years
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics, Medical, Tobacco/Alcohol History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X[i]	
Trial Treatment Administration		X	X	X	X	X	X	X	X		
Review Adverse Events (AEs)[c]			X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X	X	X	X
Vital Signs and Weight	X		X	X	X	X	X	X	X	X	X
ECOG Performance Status	X		X	X	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG	X										
PT/INR and aPTT	X										
CBC with Differential	X		X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X		X	X	X	X	X	X	X	X	
Urinalysis	X										
T3, FT4 and TSH[d]	X			X		X		X		X	
Tumor Imaging[e]	X			X		X				X	X
Videostroboscopy[e]	X			X		X				X	X
Laryngeal exam[e,f]	X					X				X	X
Modified Barium Swallow (MBS)[e]	X					X					X

Trial Period:	Screening Phase	Treatment								Post-Treatment	
Treatment Cycle/Title:		1	2	3	4	5[a]	6[a]	7[a]	8[a]	Follow Up Visits[b]	
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	3 weeks (± 1 week) after last cycle of treatment	Every 6-12 weeks (± 1 week) up to 2 years
Archival or Newly Obtained Tissue Collection[e]	X					X					
Patient-reported outcomes (PROs)[g]	X		X	X	X	X	X	X	X	X	X
Correlative Studies Blood Collection[h]	X			X		X				X	X

a Cycle 5 to 8 consists of pembrolizumab single agent for patients who achieved a pathologic complete response (pCR).

b Time of initiation and frequency of follow-up visits and procedures (videostroboscopy and fiberoptic laryngeal exam) will depend on patient's outcome following systemic therapy. For patients who did not achieve a pCR, the follow-up visits will occur after standard of care (radiation therapy plus or minus chemotherapy or surgery).

c During the Post-Treatment period, AEs will be reviewed through 90 days following cessation of treatment or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. Persistent SAE will be followed until resolution or stabilization.

d T3 will be measured at the Screening Phase. During the Treatment Phase, only TSH and FT4 will be checked prior to each treatment cycle. T3 will only be repeated at the discretion of the treating physician, if abnormalities on TSH or FT4 are noted during treatment.

e Procedures such as videostoboscopy, laryngeal exam and biopsy will be obtained prior to administration of treatment during the treatment period. Archival tissue is allowable at screening but biopsy is mandatory prior to cycle 5 for patients without progression after 2 cycles. The window for the procedures is (± 2 weeks). Post-treatment MBS occur at 3-6 months and 18-24 months after end of locoregional therapy. For patient who achieve a pathologic complete response, the post-treatment MBS will occur only at 3-6 months.

f Laryngeal exam includes operative direct laryngoscopy after 4 cycles of systemic therapy, and fiberoptic laryngeal examination during follow-up.

g PROs will be collected every 12 weeks (± 1 week) during follow-up.

hIn the Post-Treatment phase, one additional blood collection for correlative studies will happen at the 1 year time-point (± 6 weeks), and/or at the time of progression, if it occurs. Only patients who receive 6 cycles of systemic therapy will have a blood collection for correlative studies at the first follow-up visit.

i Concomitant medications will be recorded up to 30 days following the last dose of study treatment.

7.1 TRIAL PROCEDURES

7.2 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 Merck 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.

7.2.1 Clinical Procedures/Assessments

7.2.1.1 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT) and magnetic resonance (MRI). If only one test can be done, CT will be prioritized. The head and neck should be imaged at all time points specified at the Study Flow Chart. A CT chest or PET-CT will be required only at Screening. If only one image modality can be done (CT or MRI), the same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Expedited confirmation of measurable disease based on RECIST 1.1 (by CT/MRI imaging or videostroboscopy picture) at Screening should be used to determine participant eligibility.

Immobilization

For reproducibility of imaging acquisition, and since we expect 60-70% of patients will require radiation therapy, patients will be positioned in a stable supine position capable of allowing accurate reproducibility of the target position between treatments. An immobilization scheme include dedicated head and neck coils, a flat insert table with an indexed base plate, an individualized dental immobilization apparatus, and a thermoplastic head and shoulder mask.

Simulation

All patients will receive an initial standard CT simulation which will cover the head and neck with an adequate margin for generation of digitally reconstructed radiographs (DRRs) and treatment planning with non-coplanar fields. Patients will also receive a pre-therapy immobilized MR-simulation, which will be co-registered to the CT simulation. Preferably, dual energy CT scans with acquisitions at 80/100/120/140 kVp can be acquired for the contrast CT, ideally with reconstruction of ≤2mm.

All used images are to be acquired, whenever possible, in the treatment position. At a minimum, one non-MRI imaging modality (i.e. contrast CT or PET-CT) should be obtained in

treatment immobilization and coregistered with the simulation MRI, which must be performed in the treatment position. Patients will be planned for MR-simulation serially on treatment as per Study Flow Chart, which will be registered to the CT study closest to that time point.

7.1.1.1.1 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.

7.2.1.2 Assessment of pathologic complete response (pCR)

After completion of cycle 4, patients will undergo imaging (same as baseline, preferably a computed tomography). Subjects will then undergo operative direct laryngoscopy, tumor mapping, and biopsy of any residual abnormality in the operating room. If no gross residual tumor is present, biopsies will be taken at the site of the tumor epicenter (based on pretreatment videostroboscopy) and adjacent mucosa. For patients with an endoscopic and histologic complete response (pCR), four additional cycles of pembrolizumab single agent will be administered. Patients with residual disease will proceed with local therapy.

7.2.1.3 Preferred treatment for patients who do not achieve a pCR

After 4 cycles of systemic therapy, patients who achieve a partial response should proceed with single modality radiation therapy. Concurrent systemic therapy and radiation (ideally with cisplatin or cetuximab) or surgery will be the treatment of choice and strongly encouraged in patients who experience stable disease or disease progression after 2 or 4 cycles of induction pembrolizumab, cisplatin and docetaxel. The decision between concurrent systemic therapy and radiotherapy versus surgery will be based on the best judgement of the treating physicians and multidisciplinary consensus.

The preferred cisplatin dosing and schedule during concurrent chemoradiation is 40 mg/m^2 once a week (Q1W) for 6-7 doses. When cetuximab is chosen, loading dose of 400 mg/m^2 should be administered within 1 week prior to the initiation of radiation therapy, followed by 250 mg/m^2 IV Q1W for 6-7 doses. Alternative regimens (less preferably) include cisplatin 100 mg/m^2 Q3W for 2-3 doses or carboplatin AUC 2 IV Q1W for 6-7 doses during radiotherapy.

Radiotherapy will be delivered according to institutional guidelines. IMRT or protons is allowed.

7.2.1.4 Videostroboscopy and Fiberoptic Laryngeal Examination

Videostroboscopy and Fiberoptic Laryngeal Examination will be performed as per institutional guidelines at the time points specified in the Study Flow Chart. If the primary tumor is not clearly visualized by imaging of the head and neck, a picture of the lesion will be taken during the videostroboscopy procedure and will be used for comparison and response assessment throughout treatment.

7.2.1.5 Modified Barium Swallow

Modified barium swallow (MBS) will be performed at the time points specified in the Study Flow Chart. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) will be used to assess dysphagia [34].

7.2.1.6 Patient-reported outcomes (PROs)

Symptom burden will be assessed by the validated MDASI-HN[35] at multiple time points, as outlined in the Study Flow Chart.

7.2.1.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Available tissue will be mandatory for participation in the study. A biopsy will be mandatory prior to cycle 5 of treatment for patients who do not progress after 2 cycles of systemic therapy. Blood for future biomarker analysis will be drawn prior to cycle 1 (baseline), at the two re-staging image time-points (after 2 and 4 cycles of systemic therapy), and approximately 1 year after completion of curative intent treatment. For patients who achieve a pCR after 4 cycles of systemic therapy, an additional blood drawn will occur at the first follow-up visit (after 6 cycles of treatment). At each timepoint, blood will be collected for cfDNA (20 mL), EDTA plasma (10 mL) and PBMCs (40 mL) and will be processed and stored according to our department's approved laboratory standard operating procedure by Dr. Hai Tran's laboratory staff.

Biospecimens collected (including archival and newly obtained tissue and blood) will be used for correlative studies. As part of the study, a biospecimen repository will be created. The objective of this repository will be to provide material for future evaluations of relevant biomarkers that may be associated with clinical outcomes.

Tumor biomarker included in this proposal is PD-L1 expression by immunohistochemistry (clone 22C3). Additional tumor and blood biomarkers such as profiling of the tumor immune microenvironment by IHC including quantitative assessment of CD8 T cells, immune gene expression signatures by NanoString, multiplex measurement of cytokines and other soluble immune mediators, and other biomarkers that may emerge to be important for the use of checkpoint inhibitors might be evaluated according to the relevance in the literature, pending additional funding (grant submission once clinical trial is near completion/specimen are available).

7.2.1.8 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 8.

Table 8 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	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		
	Glucose		Blood for correlative studies
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

Laboratory tests for screening can be used for treatment if performed within 28 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.

7.3 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 Merck's product, is also an adverse event. All AEs will be recorded in a database (DMI) created specifically for this protocol. The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all the adverse events for subjects enrolled.

Adverse events may occur during the course of the use of Merck 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 first protocol specific intervention must be reported by the investigator. For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned procedures (e.g., usual pain, usual bleeding, and other clinically insignificant laboratory abnormalities) will not be captured and/or reported.

● All AEs will be followed/reported through 90 days following cessation of study treatment.. For patients who initiate a new anticancer therapy before 90 days following cessation of study treatment, AEs will be reported through 30 days following cessation of study treatment or until the day the new anticancer treatment is initiated, whichever is longer.

● All pregnancies and exposure during breastfeeding, from the time of treatment initiation through 150 days following cessation of study treatment must be reported by the investigator. For patients who initiate a new anticancer therapy before 150 days following cessation of study treatment, pregnancies and exposure during breastfeeding will be reported until 30 days following cessation of study treatment or until the day the new anticancer treatment is initiated, whichever is longer.

● 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 Merck.

7.3.1 Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it
- occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
-

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional
- Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IRB, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the IRB.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until **90 days** after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.3.1 Definition and Reporting of an Overdose for This Protocol

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 Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck'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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.3.2 Reporting of Pregnancy and Lactation

Although pregnancy and infant exposure during breastfeeding 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 initiation 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, or a procedure.

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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.3.3 Immediate Reporting of Adverse Events

7.3.3.1 Serious Adverse Events

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

7.3.3.1.1 Results in death;

7.3.3.1.2 Is life threatening;
7.3.3.1.3 Results in persistent or significant disability/incapacity;
7.3.3.1.4 Results in or prolongs an existing inpatient hospitalization;
7.3.3.1.5 Is a congenital anomaly/birth defect;
7.3.3.1.6 Is an other important medical event

7.3.3.1.7 **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 Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

7.3.3.1.8 Is a new cancer (that is not a condition of the study);
7.3.3.1.9 Is associated with an overdose.

Refer to Table 9 for additional details regarding each of the above criteria.

7.3.3.2 Merck Serious Adverse Events Reporting

For the time period beginning when the consent form is signed until treatment allocation, 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 2 working days to Merck Global Safety.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck 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 Merck Global Safety.

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

It is the responsibility of the PI to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the Merck's guidelines, and Institutional Review Board policy. 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 Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.3.3.3 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 the Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning at treatment initiation 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 Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck 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 5X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 3X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 3X 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.

7.3.4 Evaluating Adverse Events

The principal investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. 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 9 Evaluating Adverse Events

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

V5 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 Merck 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 Merck 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 Merck 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 Merck 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 Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck 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 Merck 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 Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck 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 Merck 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 MERCK PRODUCT, OR IF REEXPOSURE TO MERCK 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 Merck 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 Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	

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

8.1 STATISTICAL ANALYSIS PLAN

8.2 Sample Size Calculation

The study two co-primary endpoints are:

- Disease Control Rate (DCR) after two cycle of Pembrolizumab, Cisplatin and Docetaxel (PCD), AND

- Pathologic Complete Response rate (pCR) after 4 cycles of PCD.

We simultaneously monitor two co-primary efficacy endpoints using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). The null hypothesis assumes a DCR of 65% and a pCR rate of 15%. The alternative hypothesis assume a DCR of 85% and a pCR rate of 30%. There will be an interim monitoring after 10, 15, and 20 patients are enrolled. The study will be stopped early if both endpoints do not meet efficacy criteria. The design has 10% type I error and 88% power. If the treatment works, the average N=24.6. If the treatment does not work, the averaged N=17.6. Since pCR is evaluated at a later time, we will have some patients enrolled with the DCR information but not pCR. Only the cases with complete information will be used in the interim analysis.

Specifically, let n denote the interim sample size and N denote the maximum sample size. Let Y_1 and Y_2 denote the two co-primary endpoints, with $Y_1 = 1$ and $Y_2 = 1$ indicating that patients experienced favorable treatment responses in the two respective endpoints. We assume that the joint distribution of (Y_1, Y_2) follows a multinomial distribution with 4 elementary outcomes: (Y_1, Y_2) = (1, 1), (1, 0), (0, 1) and (0, 0). Let $p_1 = Pr(Y_1 = 1)$, $p_2 = Pr(Y_2 = 1)$, and define the null hypothesis $H_0: p_1 \leq 0.65$ and $p_2 \leq 0.15$, representing that the treatment is inefficacious in both co-primary endpoints. We will stop enrolling patients and claim the treatment is not promising if

$$Pr(p_1 > 0.65|data) < \lambda(\frac{n}{N})^{\alpha},$$

AND

$$Pr(p_2 > 0.15|data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ=0.95 and α=0.8 are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis $H_1: p_1 = 0.85$ and $p_2 = 0.3$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Dirichlet prior distribution $Dir(0.149,0.501,0.001,0.349)$ for the treatment effect, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.8785 under H_1:

Table 10: Optimized stopping boundaries

# patients treated	Stop if # Eff1 <=	AND # Eff2 <=
10	6	1
15	10	2
20	14	4
25	19	7

Based on Table 1, we perform the interim analysis when the number of enrolled patients reaches 10, 15, 20. When the total number of patients reaches the maximum sample size of 25, we reject the null hypothesis and conclude that the treatment is promising if the number of responses in first endpoint are greater than 19, or the number of responses in second endpoint are greater than 7; otherwise we conclude that the treatment is not promising. Below (Table 11) are the operating characteristics of the design based on 10000 simulations using the BOP2 web application, which is available at http://www.trialdesign.org.

Table 11: Operating characteristics for monitoring treatment efficacy

Pr(Eff1)	Pr(Eff2)	Pr(Eff1 & Eff2)	Early stopping (%)	Claim promising (%)	Sample size
0.65	0.15	0.149	68.73	9.80	17.6
0.85	0.30	0.299	4.49	87.85	24.5

Regarding interim monitoring, we will suspend patient accrual if the observed efficacy outcomes do not exceed the stopping boundaries. For example, when there are 10 patients treated, the stopping boundaries are if there are 6 or less disease control (DC) and 1 or less pathologic complete response (pCR). After treating 10 patients, if we see at least 7 patients with DC or at least 2 patients with pCR, we will proceed to enroll the next 5 patients even when the outcomes of some patients may still be pending. On the other hand, if we have not seen at least 7 DC's or 2 pCR's, we will suspend the patient accrual until a decision can be rendered to proceed or stop the trial.

8.3 Monitoring Plan for unacceptable level of toxicity

A dose limiting toxicity (DLT) will be defined as Grade 4 neutropenia lasting ≥ 7 days, Grade 3 or 4 febrile neutropenia, Grade 4 anemia, Grade 4 thrombocytopenia or any non-hematologic toxicity Grade 3 or greater that per Principal Investigator judgement is clinically significant and either

possibly, probably or definitely attributable to study therapy. Exceptions include grade 3 infusion reactions that resolve within 24 hours, grade 3 diarrhea, nausea, and/or vomiting that responds to standard medical treatment within 48 hours, grade 3 electrolyte disturbances that respond to correction within 24 hours), and grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic. Bayesian toxicity monitoring will be applied to ensure patient safety. Unacceptable toxicity is defined as 30% or more of the patients experiencing DLT. When Probability (unacceptable toxicity) > 0.8, patient accrual will be suspended and the clinical team will review the safety data to determine whether and how to proceed, e.g., dose de-escalation or stopping the trial. Toxicity monitoring will start from 6 patients with a cohort size of 1. Toxicity monitoring will be done during first two cycle of chemo-immunotherapy combination. The toxicity boundaries for DLT in which the regimen is considered too toxic are at least: 3 in 6, 4 in 7-8, 5 in 9-11, 6 in 12-14, 7 in 15-17, 8 in 18-20, 9 in 21-23, and 10 in 24-25 patients. The operating characteristics of the toxicity monitoring is shown in the Table12 in three scenarios when the true probabilities of toxicity are 0.1, 0.2, and 0.3, respectively. The calculation was based on the Shiny application "Bayesian Toxicity Monitoring v2.1.1" available at www.trialdesign.org.

Table 12. Operating characteristics of toxicity monitoring

Scenario	Prob.Of.Tox	Prob.Early.Sto	Prob.Declare.T	Avg.N.Patient	Avg.N.Tox
1	0.1	0.018	0.018	24.67	2.47
2	0.3	0.434	0.439	18.23	5.47
3	0.5	0.943	0.949	9.14	4.57

8.3 Statistical Analysis Plan

The co-primary endpoints of the study are the disease control rate (DCR) and the pathological complete response rate (pCR). The primary endpoints will be analyzed based on the BOP2 design as described above.

The secondary endpoints include the safety and tolerability, the laryngeal preservation rate at 2 years, the relapse-free survival at 2 years in all patients and in patients achieved pCR, and the patient-reported outcomes in patients treated with PCD. Additional exploratory objective is to assess predictive tissue and blood-based biomarkers of benefit from PCD in larynx SCC.

In general, for both the primary endpoint and secondary endpoints, exploratory data analysis and graphical methods will be applied as the first step to examine the distribution of the data, error checking, and outlier identification. Range check and consistency check will be applied to ensure the data quality. Descriptive statistics will be provided to summarize the data. Toxicity data will be summarized by frequency tables. Standard distribution plots such as the histogram

and box-plot will be applied for continuous data. The time-to-event endpoints will be estimated by the Kaplan-Meier method. Median survival, two-year rate, and the corresponding 95%

confidence intervals will be calculated. Standard statistical methods for analyzing continuous data, discrete data, and survival data will be applied whenever appropriate.

Patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as frequency distribution, mean (± s.d.) and median (range) accompanied by graphical analysis. Student t-test/Wilcoxon test and ANOVA/Kruskal- Wallis test will be used to compare continuous variables between different groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables. Log-rank test and Cox regression will be applied to time-to-event data whenever appropriate.
8.1.1.1.1

8.1.1.1.2 **Reference**

Zhou, H., Lee, J. J., & Yuan, Y. (2017). BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. *Statistics in Medicine*, 36(21):3302-3314.

9.1 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.2 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. Cisplatin, Carboplatin, and Docetaxel are standard of care therapeutic agents.

Pembrolizumab will be provided by Merck as summarized in Table 13.

Table 13 Product Descriptions

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

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-assess 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 Merck 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 APPENDICES

10.1ECOG 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.	

10.2Common Terminology Criteria for Adverse Events V5 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

10.3Contraceptive 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 14 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 14 during the protocol-defined time frame in Section 5.1.1.

Table 14 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). 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 150 days 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. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4 Larynx cancer TNM staging AJCC 8th Edition

Primary tumor (T)	
Supraglottis	
T category	**T criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Glottis	
T category	**T criteria**

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis

T category	T criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced

T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Regional lymph nodes (N)

Clinical N (cN)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); **or** Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–); **or** Metastasis in any lymph node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–)

N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)

NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

Pathological N (pN)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); **or** Larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); **or** In bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); **or** Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–); **or** Metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); **or** Multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); **or** A single contralateral node of any size and ENE(+)

N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); **or** Multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); **or** A single contralateral node of any size and ENE(+)
NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).	

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; ENE: extranodal extension.

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