Title: Induction TPN Followed by Nivolumab With Radiation in Locoregionally Advanced Laryngeal and Hypopharyngeal Cancer

NCT Number: NCT03894891

IRB Approval Date: 4/28/2020

NCI Protocol #: *N/A*

DF/HCC Protocol #: *18-652*

TITLE: Sequential therapy with induction TPN followed by nivolumab with radiation in locoregionally advanced laryngeal and hypopharyngeal cancer

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Agent(s): *Nivolumab; supplied by Bristol-Myers Squibb*

IND #: *140607*

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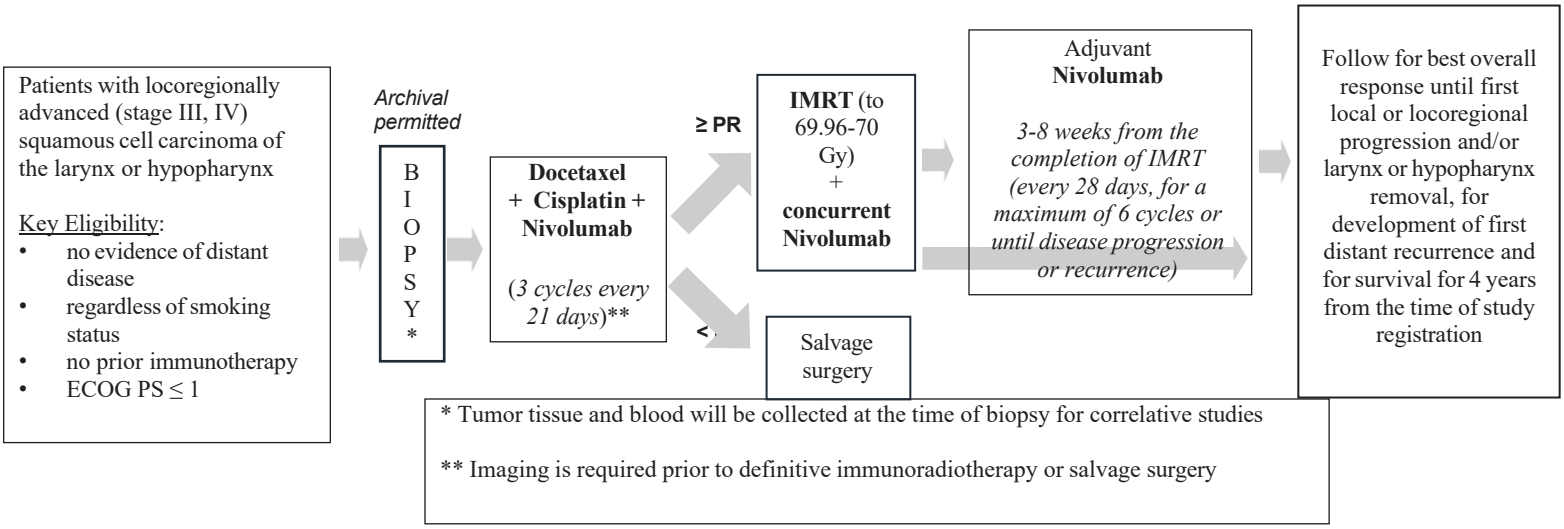
Protocol Version # / Version Date: *Amendment 2/January 28, 2020*

SCHEMA


Patients with locoregionally advanced (stage III, IV) squamous cell carcinoma of the larynx or hypopharynx
Key Eligibility:
• no evidence of distant disease
• regardless of smoking status
• no prior immunotherapy
• ECOG PS ≤ 1
Archival permitted
BIOPSY *
Docetaxel + Cisplatin + Nivolumab
(3 cycles every 21 days)**
≥ PR
IMRT (to 69.96-70 Gy) + concurrent Nivolumab
Adjuvant Nivolumab
3-8 weeks from the completion of IMRT (every 28 days, for a maximum of 6 cycles or until disease progression or recurrence)
Follow for best overall response until first local or locoregional progression and/or larynx or hypopharynx removal, for development of first distant recurrence and for survival for 4 years from the time of study registration
Salvage surgery
* Tumor tissue and blood will be collected at the time of biopsy for correlative studies
** Imaging is required prior to definitive immunoradiotherapy or salvage surgery

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1. OBJECTIVES

1.1 Study Design

This is a phase II, open label, non-randomized, multi-institutional study of nivolumab (anti-PD-1) incorporated into a definitive immunoradiotherapy program following modified induction chemotherapy using nivolumab for locoregionally advanced larynx and hypopharynx squamous cell carcinoma of the head and neck (SCCHN). Patients with confirmed locoregionally advanced SCCHN arising in the larynx or hypopharynx will receive 2-3 cycles of induction docetaxel (T), cisplatin (P) and nivolumab (N) every 3 weeks followed by clinical and radiologic assessment of response. Patients with at least a partial response (PR) defined by RECIST 1.1 will proceed with immunoradiotherapy concurrently with nivolumab. This will then be followed by an adjuvant phase of nivolumab dosed every 28 days for up to 6-cycles or until disease progression or recurrence. Those patients with less than a PR to induction TPN will be offered salvage laryngectomy and/or pharyngectomy. The primary objective of this study is to improve efficacy with respect to the endpoint of laryngectomy-free survival (LFS) in this population. The primary endpoint is to evaluate LFS at 2-years from study registration. Secondary endpoints will include overall survival (OS), locoregional control rate (LRC), and laryngo-esophageal dysfunction-free survival (LEDFS).

We hypothesize that the combination of nivolumab and radiotherapy used as definitive treatment following induction TPN in patients with locoregionally SCCHN arising in the larynx or hypopharynx will improve 2-year LFS relative to sequential induction TP + 5-fluorouracil (F) followed by platinum-based chemoradiotherapy.

1.2 Primary Objectives

- To improve efficacy with respect to laryngectomy-free survival (LFS) at 2-years from time of study registration as the primary endpoint.

1.3 Secondary Objectives

- To evaluate clinicopathologic and radiologic response
- To estimate OS
- To estimate LEDFS
- To evaluate safety and toxicity, and quality of life scores
- To characterize distinct tumor immunophentoypes and correlate these findings with outcomes

2. BACKGROUND

2.1 Study Disease

There are roughly 13,000 cases of laryngeal cancer each year in the United States, the majority of which arise in the supraglottic or glottic region [1]. Hypopharyngeal cancers arise in the pharyngeal wall, piriform sinuses, and post-cricoid region which encompasses the lateral, inferior, and posterior borders of

the larynx, respectively – but overall are less common. While cancers arising along the vocal cords or glottic region can present with early-stage disease due to the recognition of dysphonia or voice hoarseness, supraglottic and hypopharyngeal cancers are often detected in the locoregionally advanced stages given the delay in symptom development and the rich lymphatic drainage of this anatomic region.

The treatment approach to locoregionally advanced laryngeal and hypopharyngeal cancers is complex: with treatment guided by the anatomic location and extent of the tumor, along with patient-specific circumstances (such as age, functional status, psychosocial elements, and comorbid medical conditions). Input from a multidisciplinary team that includes a medical oncologist, radiation oncologist, and head & neck surgeon is crucial to individualizing the treatment strategy [2]. Functional organ preservation has been favored in recent years, owing to several landmark studies demonstrating that larynx preservation rates (LPR) are favorable with a non-surgical treatment approach without jeopardizing survival outcomes [3-4]. A series of trials have clarified that definitive concurrent platinum-based chemoradiotherapy (CRT) or a sequential treatment approach using induction chemotherapy followed by definitive CRT offers similar outcomes in locoregionally advanced laryngeal and hypopharyngeal cancers [5]. The favored regimen for induction chemotherapy has been established: a combination of a taxane added to a platinum-fluoropyrimidine backbone [6-9]. While neither definitive CRT nor sequential therapy are superior, induction chemotherapy might be favored in those with bulky primary tumors or in those with low cervical neck adenopathy owing to the risk of distant metastatic spread [10]. Despite the treatment options summarized above, 5- and 10-year overall survival (OS) rates for locoregionally advanced laryngeal and hypopharyngeal cancer patients are guarded (5-year OS: 54-58%, 10-year OS: 28-39%). These outcomes speak to the significant rate of locoregional failure in this population, with surgery offered as a salvage strategy in appropriate patients [11].

2.2 IND Agent

2.2.1 Nivolumab

2.2.1.1 Mechanism of action and pharmacology

It has become evident that tumor progression is promoted by immune evasion and abrogation of an effective immune response against cancer cells [6]. Mechanisms of tumor evasion include the development of T cell tolerance, modulation of inflammatory and angiogenic cytokines, downregulation of antigen-processing machinery, and changes in immune checkpoint receptor ligands or receptors that can all facilitate tumor immune evasion [7-9]. These mechanisms serve to define immunotherapy targets for clinical development. Immune checkpoint receptors block normal T cell activation and costimulation to maintain a homeostatic immune response [10]. Programmed cell death protein-1 (PD-1, CD279), one such receptor, is expressed on the surface of immune cells and interact with its cognate ligands on antigen-presenting or tumor cells. High tumor expression of the ligands of PD-1 (PD-L1 or B7-H1/CD274 and PD-L2 or B7-DC/CD273) and/or PD-1 expression by T lymphocytes can attenuate T cell activation and drive T cell exhaustion to favor tumor immune evasion [11]. By modulating these inhibitory immune receptor-ligand interactions, the goal is to overcome tumor mediated immunosuppression and facilitate an anti-tumor response. Preclinical evidence to support the negative regulatory effects of PD-1 comes from murine models. PD-1 knockout mice develop organ-specific autoimmunity which can mimic known autoimmune disease, such as systemic lupus erythematosus and acute graft versus host disease (GVHD) – but this can present at various time points and relies on host genetic factors [12]. Beyond PD-1 deficient

models, antibody blockade in several mouse models have demonstrated the emergence of similar autoimmune phenomena [13]. These findings strengthen the argument that PD-1 inhibition permits enhancement of antigen-specific T cell response, but also indicate that responses can be variable and depend largely on underlying host biology.

Efforts have focused on understanding PD-1/L1 expression patterns among various tumor types, in order to predict benefit from PD-1 blocking mechanisms. While estimates of tumor cell PD-L1 expression vary considerably based on tumor type [14, 15], studies have estimated PD-L1 expression in SCCHN at 30–70% with human papillomavirus (HPV) positive tumors more frequently harboring infiltrating immune cells that express PD-1 [16, 17]. Upregulation of PD-L1 expression by tumor cells may offer a strategy for evasion and protect the cell from apoptotic demise mediated by T cells, and itself may facilitate T cell apoptosis [18]. Additionally, elevated PD-L1 expression levels correlate with a poor prognosis in some solid tumor malignancies [19]. However, several studies have demonstrated that even tumors with minimal PD-L1 expression may respond to PD-1 focused inhibitory mechanisms, and thus PD-1:L1 interactions are only one component that dictate response to these inhibitory immune signals in a complex tumor immune microenvironment [20, 21].

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal antibody targeting the PD-1 or CD279 cell surface receptor that binds to PD-1 with nanomolar affinity and a high degree of specificity. This therefore precludes binding to cognate ligands, PD-L1 or PD-L2 [22]. In chronic simian immunodeficiency virus (SIV) infection in macaques, studies have shown that PD-1 blockade using an antibody to PD-1 was well tolerated and resulted in rapid expansion of virus-specific CD8 T cells [23]. PD-1 blockade also resulted in proliferation of memory B cells and increases in SIV envelope-specific antibody. These improved immune responses were associated with significant reductions in plasma viral load and also prolonged the survival of SIV-infected macaques. In vitro assays have demonstrated the ability of nivolumab to potently enhance T-cell response and cytokine production (such as interferon alpha release); when later given to cynomolgus macaques at high concentrations, there were no adverse immune-related events, independent of circulating levels of anti-nivolumab antibodies [24]. In intravenous (IV) repeat-dose toxicology studies in cynomolgus macaques, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses.

The pharmacokinetics of nivolumab have been reported in human subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as subsequent doses at 2 or 3 week intervals. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The population pharmacokinetic (PPK) analysis suggested that the following factors had no clinically meaningful effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, and PD-L1 expression. Although patient performance status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment did have a mild effect on nivolumab clearance, the effect was not clinically meaningful [22]. Additionally, PPK and exposure response analyses have been performed to support the use of 240 mg IV flat dosing every 2 weeks in addition to the 3 mg/kg every 2 week regimen. Using the PPK model, exposure to

nivolumab at 240 mg IV flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg.

2.2.1.2 Clinical safety

In an early phase I study investigating a single IV infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg (for a total of 39 patients), treatment was well tolerated. There was one serious adverse event, inflammatory colitis, observed in a patient with melanoma who received five doses at 1 mg/kg [25].

In a large registration trial which randomized advanced, platinum-refractory SCCHN patients to either nivolumab or single-agent standard chemotherapy, treatment-related grade 3 or 4 adverse events occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard arm [26]. In the nivolumab treated group, the most common adverse events were fatigue, nausea, rash, decreased appetite, and pruritis. Gastrointestinal events were less common than with standard chemotherapy. Pneumonitis was observed in 2.1% of nivolumab-treated patients and two treatment-related deaths occurred (one from hypercalcemia and one from pneumonitis).

The overall safety experience with nivolumab as monotherapy is based on experience from more than 8,000 subjects treated to-date in patients with varied cancer types. The safety profile appears similar across cancer types [27, 28]. Treatment-related adverse events of grade 3 or 4 were reported in 7% of patients treated with nivolumab in advanced non-small cell lung cancer (NSCLC) of squamous histology and in 16.3% of unresectable, advanced stage melanoma patients.

The safety of combining PD-1 inhibition with radiation therapy (RT) has been demonstrated in several reports and is being investigated in several ongoing clinical trials. Fiorica and colleagues showed the safety of nivolumab with definitive RT retrospectively in 35 patients treated with anti-PD-1 therapy after hypofractionated RT at an interval of at least 1 week from the end of RT [34]. Toxicity rates between patients receiving RT alone and the combination of nivolumab-RT were similar.

2.2.1.3 Clinical efficacy

Results from an early phase I trial demonstrated a wide range of clinical activity, including complete, partial and mixed response rates in advanced solid tumor patients; including individuals with colorectal cancer, NSCLC, melanoma, and renal cell carcinoma (RCC) [25]. Thirty-nine patients received a single IV infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg. Patients with evidence of clinical benefit at 3 months were eligible for repeated therapy. One durable complete response (CR) and two partial responses (PRs; melanoma, RCC) were observed. Two additional patients (melanoma, NSCLC) had significant tumor regression not meeting defined PR criteria. Following this early signal, numerous clinical trials emerged to investigate the clinical efficacy of nivolumab in advanced solid tumor and hematologic malignancies – with nivolumab (Opdivo™) now approved in multiple cancer types owing to its demonstrated clinical efficacy.

In a randomized phase III study (Checkmate-141) of patients with recurrent or metastatic, platinum-refractory SCCHN, 361 patients were assigned to nivolumab or standard chemotherapy in a 2:1 ratio with a primary endpoint of overall survival (OS) [26]. Nivolumab (at a dose of 3 mg/kg body weight IV) every

2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab) was administered. Additional end points included progression-free survival (PFS), objective response rate (ORR), safety, and patient-reported quality of life (QOL). The median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the group that received standard therapy. OS was significantly longer with nivolumab than with standard therapy (hazard ratio [HR] for death, 0.70; 97.73% CI, 0.51 to 0.96; p = 0.01), and the estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%). Median PFS was 2.0 months (95% CI, 1.9 to 2.1) with nivolumab versus 2.3 months (95% CI, 1.9 to 3.1) with standard therapy (HR for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; p = 0.32). The rate of PFS at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Additionally, individuals in the study who were PD-L1 (≥ 1% of tumor or immune cells by immunohistochemistry [IHC]) or HPV positive appeared to have improved outcomes. That said, regardless of PD-L1 expression or HPV status, patients treated with nivolumab experienced a reduction in the risk of death compared with standard chemotherapies. This study led to the approval of nivolumab in this setting in November of 2016.

2.3 Other Agents

Multiple trials have clarified the three-drug combination of cisplatin, fluorouracil, plus a taxane as the preferred approach when using induction chemotherapy in SCCHN. Early clinical trials found that cisplatin (100 mg/m^2 IV) and 5-fluorouracil (1000 mg/m^2/day IV continuous over a 24-hour infusion for five days) given for three cycles as induction achieved higher overall response rates and improved outcomes compared with other two-drug platinum based regimens [28]. Later trials found that the addition of a taxane (docetaxel or paclitaxel) to the platinum-doublet backbone with 5-fluorouracil enhanced efficacy. The most extensive data was from the TAX-324 trial where TPF (docetaxel 75 mg/m^2 IV day 1, cisplatin 100 mg/m^2 IV day 1, and continuous infusion 5-fluorouracil 1000 mg/m^2/day for days 1-4) was the studied regimen, which showed improved survival compared with a doublet platinum-based regimen [6,7]. Additionally, a combined meta-analysis incorporating data from 1,772 patients in 5 trials confirmed that adding a taxane to the induction regimen improved survival and decreased rates of locoregional failure [29].

Data from the locoregionally advanced, recurrent or metastatic setting supports the combination of cisplatin with docetaxel (or taxanes) without infusional 5-fluorouracil (5-FU). The EORTC performed a multicenter phase II study using cisplatin (75 mg/m^2 IV day 1) and docetaxel (100 mg/m^2 IV day 1) every 21 days and noted objective response rates of 54%, with 5 complete responses and 14 partial responses (overall response rate of 86%) among the untreated locoregionally advanced or metastatic subgroup (n = 22) [36]. Glisson and colleagues similarly demonstrated that the TP (docetaxel, cisplatin) combination yielded a 40% response rate among advanced, incurable SCCHN patients [37]. The combination of cisplatin-docetaxel has been prospectively studied as induction and has demonstrated a 70% response rate (26% CRs, 44% PRs) but with 34% of patients experiencing grade 3+ neutropenia [38]. Even in an elderly population, response rates of up to 88% have been described with the TP induction backbone, without 5-FU (F) [39]. These data support the choice of drugs and schedule of administration for TP in the current study, combined with nivolumab (N) at standard dosing to replace the 5-fluorouracil infusion which requires port-a-cath placement or inpatient admission with added toxicity concerns.

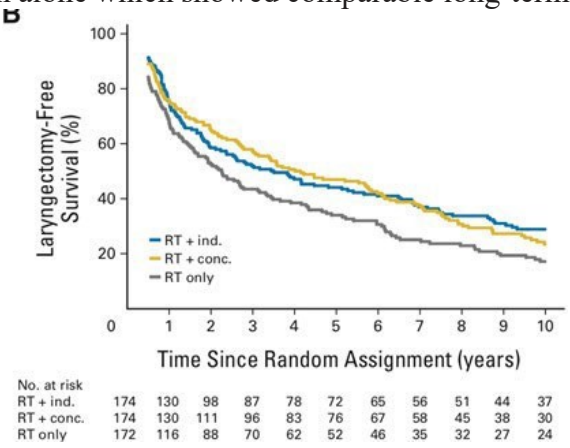
2.4 Radiation Therapy

A combined multimodality approach that incorporates both chemotherapy and radiation therapy (RT) has long been established as the backbone of definitive treatment based on the results of multiple clinical trials in SCCHN and specifically in larynx and hypopharynx cancer [3, 27]. RTOG 0129 clarified that an altered RT fractionation schedule when combined with chemotherapy did not improve outcomes. In fact, standard RT fractionation as part of a concurrent chemoradiation program appears superior [30,31]. RTOG 0129 outlined a total dose of 70 Gray (Gy) in 35 fractions over seven weeks, which is the schedule of radiation proposed in the current study – which will be concurrently administered with nivolumab as part of definitive immunoradiotherapy.

Preclinical data, particularly in melanoma, have highlighted the potential synergism when utilizing immune checkpoint blockade with RT. In fact, cases of immunotherapy exposure followed by targeted RT has shown reductions in distant tumor sites, the abscopal effect [32]. Studies have shown that tumor PD-L1 expression can increase following RT exposure and that the combination enhances anti-tumor immunity [33].

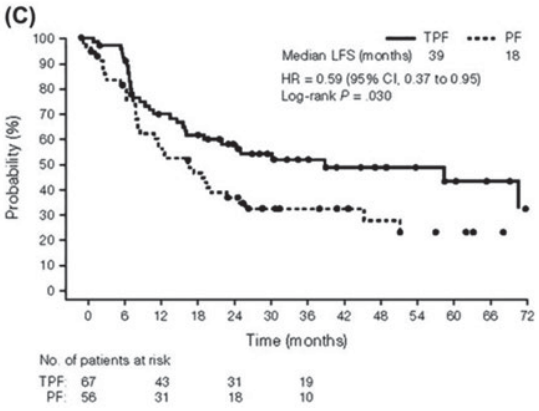
2.5 Rationale

The primary rationale for the use of induction chemotherapy (IC) in locoregionally advanced larynx and hypopharynx cancers is to avoid radical surgery. With a goal of organ preservation, two initial landmark trials published in the 1990s investigated the role of IC followed by radiation [3-4]. In both studies, patients were randomized to a platinum-5-fluorouracil (PF) IC regimen followed by radiation (permitting salvage surgery) vs. conventional laryngectomy and radiation alone. These studies demonstrated that larynx preservation was feasible (larynx preservation rate [LPR] between 40-60%) without jeopardizing long-term survival [5]. This was followed by the RTOG 91-11 study comparing a PF IC regimen followed by radiation, concurrent chemoradiation (CRT), and radiation alone which showed comparable long-term survival among all three treatment arms [11-12]. Of note, the composite endpoint of laryngectomy-free survival (LFS) was similar in both chemotherapy-containing arms (5-year LFS, IC: 44.1% vs. CRT: 47%, p = 0.68);10-year LFS, IC: 28.9% vs. CRT: 23.5%, p = 0.68) [**Figure** right]. It should be noted that the RTOG 91-11 study utilized PF (cisplatin, 5-FU) and not TPF for induction therapy. A similar study compared PF IC followed by radiation to an alternating platinum-based CRT schedule and demonstrated similar 3-year LFS rates [13]. Larynx preservation was an important milestone achieved with the use of IC, and these early trials led to updated national guidelines supporting the role of IC as an initial approach in these patients.



Early observations with taxanes in head and neck cancer then led to trials combining these agents with a PF backbone as IC. In addition, there was significant interest in using IC followed by concurrent CRT given the increase in locoregional control offered by a concomitant treatment program [12]. The TAX-324 study randomized patients with locoregionally advanced head and neck cancer, including larynx and hypopharynx tumors, to receive docetaxel plus PF (TPF) followed by concurrent CRT vs. PF followed by

the same concurrent regimen. Results showed improved overall survival in favor of the TPF arm (5-year OS, TPF: 52% vs. PF: 42%) with a manageable side effect profile [6-7], establishing TPF as the preferred IC regimen in SCCHN. Two additional trials utilized the TPF regimen specifically in larynx and hypopharynx patients: GORTEC 2000-01 randomized patients to TPF vs. PF followed by radiation if they had any initial response to IC [8] and the LPR was significantly improved favoring TPF (70.3%). TREMPLIN was a phase II study using TPF for organ preservation with responders randomly assigned to either concurrent CRT or cetuximab with radiation [9]. LPR exceeded 90% overall with no difference in larynx function preservation or survival among each arm. In the GORTEC study, larynx dysfunction-free survival (LDFFS) rates favored the TPF arm in long-term follow-up (5-year LDFFS, TPF: 67.2% vs. PF: 46.5%) [14]. TPF followed by either radiation or concurrent CRT is an acceptable approach for organ preservation based on these results, with TPF followed by radiation favored in Europe.



It is now widely recognized that tumors harbor immune checkpoint receptors to escape immune recognition, and immune checkpoint receptor inhibitors that block inhibitory immune cell interactions have demonstrated efficacy in advanced head and neck cancer [16-17] prompting clinical trials to explore their potential in other head and neck cancer populations. Recognizing that the risk of toxicity can be significant with TPF IC followed by chemoradiotherapy (so-called sequential treatment), and in the hopes of improving LFS here we propose a multicenter, non-randomized phase II study replacing 5-fluorouracil in TPF with the anti-PD-1 inhibitor nivolumab as TPN followed by definitive intensity-modulated radiation therapy (IMRT) with nivolumab and subsequent adjuvant PD-1 blockade. The rationale for using 2-3 induction doses of immunotherapy with a TP backbone stems from early studies showing that few doses of checkpoint blockade may be all that is necessary to trigger immunomodulation prior to definitive therapy [35]. Maintaining a platinum-taxane based IC regimen and adding active immunotherapy is aimed at decreasing cytotoxic side effects while preserving response rates and improving patient tolerability (such as avoiding a port-a-cath or committing the patient to infusional therapy). Several trials have combined taxane-platinum combinations alone (specifically docetaxel, cisplatin or TP) in the advanced setting and untreated, locoregionally advanced setting with favorable efficacy [37, 40-41]– including an 86% overall response among untreated locoregionally advanced and metastatic patients [36]. More recent studies have investigated docetaxel-cisplatin (TP) induction and together have shown overall response rates to induction TP of 70-88%, but with notable rates of neutropenia [38-39]. Given rates of grade 3+ neutropenia in many docetaxel-cisplatin (TP) trials, we favor the option of granulocyte-colony stimulating factor (GCSF) support in combination with PD-1 blockade in the current study.

Posner and colleagues published a further analysis of the TAX-324 data in 2009 [42] which was aimed at characterizing LFS rates among TPF treated patients. Among operable stage III and IV larynx or hypopharynx cancer patients in their analysis (n = 123), the 3-year LFS rate was significantly higher among patients who received induction TPF (52%) vs. PF (32%) in TAX-324 [**Figure** below right]. Further, the 2-year LFS rate among the TPF arm was 58% vs. 37% in the PF arm. The authors note they chose the *operable* TAX-324 subgroup and not the entire cohort because they wanted to more closely represent the populations studied in prior trials (RTOG 91-11, EORTC 24594, and GORTEC 2000-01).

They make the point that TAX-324 included patients with more advanced primary tumors and nodal disease than these other trials. They also suggest that using the LFS endpoint in an *inoperable* population is not feasible since inoperable patients don't have a surgical salvage option and would present with more advanced disease characteristics. Finally, the authors point out that the lower 2-year LFS results in this TAX-324 subanalysis for the PF arm (37%) as compared to RTOG 91-11 (2-year LFS for the PF arm was 60%) resulted from the more liberal entry criteria for TAX-324 which allowed patients with borderline operable or more advanced disease. Since the proposed trial using induction TPN will not select patients based on upfront operability (and therefore may enroll a more advanced stage cohort) and will select HPV negative participants, we consider a 2-year LFS estimate of 55% for induction TPF both reasonable and conservative for comparison.

In summary, we hope to demonstrate an improvement in the 2-year LFS rate compared with the preferred sequential therapy approach of TPF followed by CRT. Secondary endpoints will include OS at 2-years and the important composite endpoint of laryngo-esophageal dysfunction-free survival (LEDFS) at 2-years which attempts to capture long-term, patient-focused functional outcomes. If this immunotherapy-based sequential treatment program proves beneficial, it could stand next to or replace TPF followed by definitive chemoradiotherapy.

2.6 Correlative Studies Background

Given that response rates to PD-1 blockade in the advanced, platinum-refractory SCCHN setting approach 20%, there is strong interest in identifying biomarkers that predict clinical benefit. In a NSCLC population, PD-L1 expression in at least 50% of tumor cells yielded a response rate of 45.2%, compared with an objective response rate of 19.4% among all treated patients [17]. More recently, whole-exome sequencing of NSCLC tumors treated with PD-1 blockade revealed that higher mutational burden correlated with improved objective response rates [18]. Somatic alterations in tumor cells yield neoantigens which are thought to facilitate antigen-specific CD8+ T cell responses – suggesting that the genomic landscape of the tumor impacts PD-1 response. In SCCHN, stromal or tumor PD-L1 expression does appear to partially impact response, but even PD-L1 negative patients may respond to treatment – suggesting important mechanisms beyond PD-1:L1 interactions [15, 19].

Early preclinical and clinical studies have also demonstrated potential synergy between high dose per fraction radiotherapy and immunotherapy [20]. Radiation delivered in a limited number of fractions has been shown to impact circulating immunologic cytokines and have local immunologic effects on the primary tumor [21]. Some reports even suggest that hypofractionated radiation can potentiate immunologic effects following PD-1/L1 exposure leading to responses outside the targeted radiation field (so-called abscopal effect) [22-23]. Curiously, circulating levels of activated T cells appear increased and myeloid-derived suppressor cells (MDSCs) decreased among melanoma patients with abscopal responses following radiation [22].

More recent work has sought to use more comprehensive immune-based metrics to characterize the tumor microenvironment. Cytometric profiling has identified immunologically ‘hot’ and ‘cold’ immunophenotypes which may identify tumors more likely to respond to immunotherapies [24-25]. We have demonstrated similar findings in head and neck cancer patients: showing that a robust CD8+ T cell infiltrate and pattern of immune checkpoint co-expression may predict clinical benefit to PD-1 blockade in an advanced SCCHN population [26].

3. PARTICIPANT SELECTION

Participants must meet the following eligibility criteria on screening examination to be eligible to participate in the study:

3.1 Eligibility Criteria

3.1.1 Subject must have histologically or cytologically confirmed, resectable or unresectable, Stage III or Stage IV locoregionally advanced squamous cell carcinoma of the larynx or hypopharynx, as defined by 2017 American Joint Committee on Cancer (AJCC), 8th edition

3.1.2 Willing to provide tissue from diagnostic biopsy and blood samples before, during, and after treatment

3.1.3 Any smoking history is permitted

3.1.4 Patients must have HPV negative disease. Those patients with a supraglottic primary are required to undergo HPV testing with p16 immunohistochemistry and/or confirmatory HPV PCR or ISH testing to rule out oropharyngeal origin with laryngeal extension

3.1.5 Age 18 years or older

3.1.6 ECOG performance status ≤ 1 (Karnofsky ≥ 80%, see Appendix A)

3.1.7 Participant must have normal organ and marrow function as defined below within 21 days prior to study registration:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤2.0 g/dL
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal

3.1.8 Ability to understand and the willingness to sign a written informed consent document

3.1.9 Women of childbearing potential (WOCBP) must agree to use appropriate method(s) of contraception. WOCBP should plan to use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug

3.1.10 Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 iu/l or equivalent units of hcg) within 24 hours prior to the start of nivolumab

"Women of childbearing potential (WOCBP)" is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL

3.1.11 Men who are sexually active with WOCBP must agree to use any contraceptive method with a failure rate of less than 1% per year. Men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men) do not require contraception

See Appendix B for further guidance on contraception.

3.2 Exclusion Criteria

3.2.1 Existing severe autoimmune conditions (at the discretion of the treating physician). Patients with a history of Hashimoto thyroiditis who are stable on replacement hormone therapy are not excluded. Short-term corticosteroid dosing is permitted (i.e. dexamethasone for chemotherapy-induced nausea prevention during induction chemotherapy) as long as steroids are discontinued within 1 week (7 days) of receiving the first dose of nivolumab during the induction phase of treatment.

3.2.2 Subject who has had prior chemotherapy for head and neck cancer and/or radiotherapy to the head and neck.

3.2.3 Subject who has been treated with immunotherapy. This includes prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

3.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Known human immunodeficiency virus carrier or a diagnosis of immunodeficiency. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

3.2.7 Known non-infectious pneumonitis or any history of interstitial lung disease.

3.2.8 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer, and low-risk prostate adenocarcinoma being managed with active surveillance. A history of another separate malignancy in remission without evidence of active disease in the last 5 years is permitted.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Eligible participants will be registered in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.2 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute, the Coordinating Center, by the Study Coordinator. All sites should call the Study Coordinator to verify eligibility and registration status.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.3 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and faxed or e-mailed to the Study Coordinator:

- Copy of lab results
- Signed participant consent form
- HIPAA authorization form
- Eligibility checklist

The participating site will then call or e-mail the Study Coordinator to verify eligibility. The Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration.

5. TREATMENT PLAN

Eligibility and exclusion criteria are provided in Section 3. These criteria will be assessed 21 days prior to study registration to establish eligibility and baseline values.

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments.

Demographic information and baseline characteristics will be collected at the Screening Visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG PS (Appendix A), disease status, and medical histories.

5.1 Treatment Regimen

5.1.1 C1D1 of TPN Induction Therapy

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The induction TPN cycle will be **21 days long**, and nivolumab cycles thereafter will be **28 days long**.

Below are the specific laboratory criteria patients will need to meet in order to begin a subsequent cycle of TPN (docetaxel, cisplatin and nivolumab):

- Leukocytes ≥3,000/mcL
- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Total bilirubin ≤2.0 g/dL
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- Creatinine within normal institutional limits
  OR
- Creatinine clearance ≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal
- Thyroid function tests (TSH) should be reviewed prior to the start of TPN therapy. If abnormal then replacement hormone therapy can be utilized without delaying the start of induction TPN. Thyroid function test abnormalities generally should not interrupt dosing on protocol unless the patient is severely symptomatic from hypo- or hyperthyroidism.
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 iu/l or equivalent units of hcg) within 24 hours prior to the start of nivolumab.

5.1.2 Dose and schedule of TPN Cycles, and Pre-medications

Patients with confirmed locoregionally advanced SCCHN arising in the larynx or hypopharynx will receive 3 cycles of induction docetaxel, cisplatin and nivolumab (TPN) every 3 weeks (or **21 days**), followed by clinical and radiologic assessment of response.

TPN dosing will consist of docetaxel 75 mg/m^2 IV day 1, cisplatin 100 mg/m^2 IV day 1, and nivolumab 240 mg IV flat dose day 1 of a **21 day cycle**.

Standard pre-medications including dexamethasone, palonosetron or ondansetron, and fosaprepitant are permitted for anti-emetic effect. Pre-medication with dexamethasone prior to taxane exposure is permitted and strongly encouraged.

5.1.2.1 Antibiotic prophylaxis and GCSF support

Following each TPN cycle administered, patients will receive oral levofloxacin 500 mg daily by mouth on day 5 through day 15 of the cycle for antibiotic prophylaxis.

In addition, granulocyte-colony stimulating factor (GCSF) support can be administered (at the treating physician's discretion, see *Section 2.5*) at least 24 hours (but no later than 72 hours) after completion of the TPN infusion in the form of pegfilgastrim 6 mg subcutaneously once or as tbo-filgastrim administered subcutaneously daily at least 24 hours after the completion of the TPN infusion (but no later than 72 hours). Tbo-filgastrim should be given for at least 5 days and continued for a maximum of 14 days or until the ANC is at or above 1000. Tbo-filgrastim should not be given with 24 hours of the start of the next cycle of TPN.

5.1.2.2 Dose Reductions and Delays for TPN

- If laboratory criteria are not met or patient experienced toxicity prohibits the administration of a subsequent TPN cycle, the next cycle can be **delayed** up to 14 days (2 weeks) and then resumed at chemotherapy dose attenuation (at the discretion of the treating physician and per protocol standards in *Section 6.0*).
- If laboratory criteria or treatment-related side effects limit the administration of cycle 2 of TPN for more than 14 days, the subject should be removed from the study treatment.
- If administration of cycle 3 of TPN is delayed more than 14 days, the treating physician or PI may allow the subject to proceed to the definitive radioimmunotherapy phase of treatment (i.e. 2 cycles of TPN are **required** to proceed to the definitive radioimmunotherapy phase of treatment).
- Individual cytotoxic agents (docetaxel or cisplatin) can be modified or dose reduced at the discretion of the treating physician (see *Section 6.0*), but should not be *individually* omitted from the TPN regimen. Nivolumab should not be dose reduced but rather held for patient experienced toxicity during the induction TPN phase.

5.1.3 Post-TPN Imaging for Response Assessment

Subjects will undergo repeat neck CT or MRI or PET-CT following the completion of the induction phase of treatment (**at least 10 days** after the completion of the last TPN infusion).

- *Partial or Complete Response:* Patients with a radiographic partial response (PR) defined by RECIST 1.1 following 2-3 cycles of induction TPN, will proceed with immunoradiotherapy concurrently with nivolumab.
- *Stable Disease or Progression*: Those patients in whom at least a radiographic PR is not achieved will be offered surgical salvage comprised of laryngectomy and/or pharyngectomy at the discretion of the involved head & neck surgeon, if their disease is deemed resectable. In the case of salvage surgery, the patient will not proceed with further study treatments and will receive standard post-operative radiation with or without chemotherapy off protocol. If the patient has less than a radiographic PR to induction TPN and declines salvage surgery or is deemed unresectable, the patient is likely to be considered palliative or incurable and may continue cytotoxic therapy or immunotherapy, or even consider radiation or chemoradiotherapy, at the discretion of the treating physician.

5.1.4 Concurrent Radioimmunotherapy with Nivolumab

At least 21 days or 3 weeks after completion of the last cycle (cycle 2 or 3) of TPN and after completion of reimaging, patients will start concurrent radioimmunotherapy. Intensity-modulated radiotherapy (IMRT) is preferred, and proton beam radiotherapy is not permitted. If a patient completes the induction phase of the study but elects to come off protocol for proton beam radiotherapy, this will be logged and tracked, and annually reported. Six months after study initiation, the PI and co-investigators should review proton use data.

Treatment planning CT scans should be performed with neck and shoulder immobilization that will also be used during daily treatment. Treatment planning scans should at least encompass the region from the orbits to below the clavicles. CT scan thickness should be 0.3 cm or thinner in the area of the target volumes.

5.1.4.1 Radiation Therapy Planning and Delivery

Target volumes should be delineated on each CT slice where present. The Gross Tumor Volume (GTV) is specifically defined as all known gross disease determined from pre-chemotherapy evaluations including clinical information and imaging (CT, MRI or PET). Clinical target volumes (CTV) are defined as either the GTV with an anatomical margin or areas at risk of harboring microscopic disease. Generally, these volumes will include a high-risk clinical target volume (CTV1) including volumes of potential tumor extension (adjacent to primary or nodal GTV) and nodal areas at highest risk for microscopic involvement abutting areas of gross disease. The exact margins will be determined on a case by case basis. There will also generally be a CTV2 including lymph node or other regions at lesser risk of nodal involvement. In general, the entire larynx and both sides of the neck (including most or all of levels 2-4) should be treated as part of GTV, CTV1 or CTV2 in all cases, and depending on the location of primary tumor and/or involved lymph nodes, consideration should be given to include nodal levels VI, and the upper mediastinum a tracheostomy/stoma if present, as well as levels 1b and 5 and the lateral retropharyngeal lymph nodes in the node positive neck. The planning target volumes (PTV) will provide a margin to account for variation in daily set up and are in general expected to be approximately 3-5mm. The following normal structures should also be defined and delineated in all cases: spinal cord, brainstem, right and left parotid and submandibular glands, larynx, mandible, oral cavity, esophagus, left and right brachial plexus, left and right cochlea, constrictor muscles, or postcricoid.

The GTV should be prescribed either 70 Gy in 35 fractions or 69.96 Gy in 33 fractions and CTV1 and CTV2 should be prescribed approximately between 59-63 Gy, and 46-54 Gy, respectively. Definitive immunoradiation should be delivered in 33-35 fractions with intensity-modulated radiotherapy (IMRT). Either dose-painting IMRT or a sequential boost approach are permitted. No more than 20% of the PTV should receive >110% of the prescription dose. In most cases, no more than 5% of the PTV should receive < 95% of the prescription dose.

The following normal tissue limits are recommended:

Brainstem	maximum < 54 Gy
Spinal Cord	maximum < 45 Gy
Mandible	maximum < 70 Gy
Cochlea	maximum < 30 Gy
Brachial plexus	maximum < 66 Gy
Parotid	mean dose to one of the parotid glands < 26 Gy

Note: In cases with a conflict and/or overlap between target and normal tissue, target dose considerations should take priority at the discretion of the treating physician. Exceptions to this include the brainstem and spinal cord, which take priority.

Treatment should be delivered with megavoltage equipment capable of delivering static or dynamic intensity modulation or other techniques capable of meeting dose specifications and constraints and delivering highly conformal radiation. Treatment should generally be delivered once daily, Monday-Friday, over a period of approximately 7 weeks. Treatment breaks are strongly discouraged. Images should be obtained prior to the first treatment to verify the treatment position. During treatment, imaging should be repeated at least once per week for setup verification, although daily image guided radiation therapy is

suggested.

Real time radiation plan review is not required. However, for verification purposes, it is requested that sites submit digital radiation data within two weeks following the completion of radiation therapy. This should be transferred via secure Partners Healthcare Interface (transfer.partners.org). Participating centers will be invited to create an account within this system by study staff. These data should include: treatment plan in DICOM format including the complete radiation structure set and radiation dose matrix in absolute dose, as well as supportive diagnostic imaging used to create the radiation treatment plan (e.g. imaging performed prior to induction chemotherapy); a dose volume histogram (DVH) including all treatment targets and organs at risk; and summary document(s) which includes: the date of first and last treatment, the prescribed dose to each target (GTV, CTV1, CTV2), treatment planning system, and method of IGRT, if applicable.

5.1.4.2 Radiation Timing and Schedule

The first fraction of RT should be administered no later than 6 weeks (or 42 days) after the last cycle of TPN. The planned 33-35 fractions of RT are to be administered on a continuous weekday schedule for a total of approximately 7 weeks (permitting holiday and weekend day interruptions).

5.1.4.3 Concurrent Nivolumab Dosign and Schedule with Radiation

5.1.5 Adjuvant Nivolumab Phase

5.1.6 Stopping Rules

In addition to the continuous routine toxicity monitoring by the study team throughout the duration of the trial, the following

These events and rates will be continuously monitored and decisions made regarding the overall status of the trial.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1
If screening assessments occur within a week before start of study treatment, then they may serve as the baseline or cycle 1 day 1 visit. Laboratory evaluations do not need to be repeated to meet eligibility criteria on cycle 1 day 1, if they were done within 3 days of the first treatment dose.

5.3 Chemotherapy Administration

When administering TPN cycles, the T (docetaxel) should be administered per standard institutional guidelines first, followed by a 30 minute wait period to evaluate for infusion reaction. P (cisplatin) should be administered second per institutional standards, followed by a 30 minute wait period. Nivolumab should be administered last as outlined in *Section 5.4* below, and given over 30 minutes.

For both docetaxel and cisplatin, standard operating procedure should be applied when recalculating weight-based dosing at the beginning of each cycle. Nivolumab is to be used at a flat dose.

5.4 Nivolumab Administration

5.4.1 Description of the Dosage Form

Nivolumab injection, 100 mg/10 mL (10 mg/mL): Nivolumab injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween 80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe

holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

5.4.2 Drug Product Preparation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL): Nivolumab injection is to be administered over 30 minutes (± 10 minutes) as an IV infusion through a 0.2 to 0.22 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Dilute nivolumab with either 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total infusion volume must not exceed 160 mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

5.4.3 Recommended Storage and Use Conditions

Nivolumab Injection, 100 mg/10 mL (10 mg/mL): Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 CYP 450 Drug Interactions

Because there is a potential for interaction of nivolumab with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.5.2 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids with the exception of during the induction phase of treatment for pre-medication and anti-emetic purposes

  - Note: In regards to cisplatin anti-emetic prevention: dexamethasone is permitted on days 1-4 of the induction or TPN cycle (up to 12 mg IV/po on day 1) and reduced to a total dose of 8 mg daily for up to 3 days after cisplatin dosing. Delayed emesis can be managed in a subsequent TPN cycle using dexamethasone 8 mg twice daily x 2-days followed by 4 mg twice daily x 2-days starting the day after chemotherapy dosing.
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents

5.5.3 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone equivalent) or other immunosuppressive medications within 7 days of the first dose of nivolumab treatment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses ≤ 20 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

5.5.4 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses ≤ 20 mg daily prednisone are permitted. A course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

5.6 Criteria for Taking a Participant Off Protocol Therapy

5.7 Duration of Follow Up

5.8 Criteria for Taking a Participant Off Study

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Delays or Modifications for TPN

Dose modifications for the docetaxel-cisplatin (TP) component of the TPN regimen are permitted and should follow institutional standards based on toxicity, with the following suggested modifications:

- When dose reductions in TP (docetaxel and cisplatin) occur they should include the appropriate dose level reductions of both or either agent as specified in **Table B** below (each row of Table B indicates the recommended single or dual agent reduction). In Table B, the toxicity listed in the first column on the left corresponds to the recommended dose attenuation in the middle and right columns.
- A maximum of 2 dose reductions per individual study chemotherapy drugs are permitted: if additional reductions are required, the induction TPN regimen should be discontinued.
- If this occurs in cycle 3 of the TPN phase, the patient may proceed to definitive radioimmunotherpy on protocol.
- If this occurs during cycles 1 or 2 of induction TPN, the patient will be removed from the protocol.
- Once a dose has been decreased, it should remain reduced for all subsequent dosing unless dose is further reduced. No dose escalations will be allowed.
- If one or more of the study drugs is delayed due to drug related toxicities during a treatment cycle, the other study drugs (TP or N) in the regimen may be administered at the discretion of the investigator; when dosing is resumed, dose reduction should only be applied to the study drug that was withheld.

Table A. Recommended Dose Levels:

	Cisplatin dose	**Docetaxel dose**
Starting dose	100 mg/m^2	75 mg/m^2
Dose Level -1	75 mg/m^2	56 mg/m^2
Dose Level -2	56 mg/m^2	37 mg/m^2

Table B. Recommended Dose Modifications for Toxicity:

	Cisplatin	**Docetaxel**
Neutrophils (ANC) < 500/mm^3 lasting ≥ 5 days	Decreased by -1 dose level	Decreased by -1 dose level
Febrile neutropenia (body temperature ≥ 38.5C and ANC < 1000/mm^3)	Decreased by -1 dose level	Decreased by -1 dose level
Platelets < 25,000/mm^3	Decreased by -1 dose level	Decreased by -1 dose level
Platelets < 50,000/mm^3 with significant bleeding or requiring transfusion	Decreased by -1 dose level	Decreased by -1 dose level
Grade 4 hemoglobin (< 6.5 g/100 mL)	Decreased by -1 dose level	Decreased by -1 dose level
Nausea or emesis ≥ grade 3 despite optimal medical management	Decreased by -1 dose level	Decreased by -1 dose level
Stomatitis ≥ grade 3	Decreased by -1 dose level	Decreased by -1 dose level
Diarrhea ≥ grade 3 despite optimal medical management	Decreased by -1 dose level	Decreased by -1 dose level
Neuropathy (sensory or motor) grade 2 lasting > 7 days or grade 3 lasting 7 days or less	Decreased by -1 dose level	Decreased by -1 dose level
Nephrotoxicity (creatinine clearance 50-59 mL/min or grade 3 creatinine elevation)	Decreased by -1 dose level	No modification
Total bilirubin > 1.5x ULN	No modification	No modification
Total bilirubin > 2.5x ULN	No modification	75% of previous dose
Total bilirubin > 4x ULN	No modification	50% of previous dose
Other grade ≥ 3 toxicities (except fatigue or transient arthralgias,	Decreased by -1 dose level	Decreased by -1 dose level

myalgias)		

6.2 Dose Delays for Nivolumab

There will be **no** dose reductions for nivolumab permitted. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.
Administration of nivolumab should be **delayed** for the following adverse events:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
  Note: see Appendix C for guidelines on managing immune-related toxicities

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria (as described below) are met. Participants with a delay in dosing beyond 6 weeks should be considered for discontinuation of protocol treatment and discussed with the Overall PI.

Subsequent dosing may be re-started if subjects continue to meet laboratory criteria (baseline values). The investigator will determine if subsequent dosing is appropriate for subjects who have laboratory or clinical abnormalities that do not meet dose discontinuation criteria (described below). All related grade 2 toxicities should be discussed with the Overall PI, prior to subsequent dosing.

6.2.1 Administration of nivolumab should be permanently discontinued for the following adverse events:

- Any grade encephalitis, grade 3 adrenal insufficiency, and grade 3 myocarditis, or any reoccurrence of the same grade 3 adverse reaction will require discontinuation of nivolumab.
- A grade 3 pneumonitis and grade 3 uveitis will require permanent discontinuation.
- Any grade 4 adverse event will require permanent discontinuation with the following exceptions:
  - Grade 4 electrolyte abnormalities that < 72 hours in duration
  - Grade 4 neutropenia or lymphopenia < 5 days in duration
  - Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation with the Overall PI.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Adverse Event Characteristics:

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

7.2 Adverse Event Reporting

7.2.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.2.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/. Send the SAE forms as follows:

7.2.3 For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.2.4 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

	DF/HCC Reportable Adverse Events(AEs)				
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3 Serious Adverse Events

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

7.4 Expected Toxicities

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list in the Investigator's Brochure or is included in the informed consent document as a potential risk. Most common adverse events or expected toxicities are listed below. Details are found in the respective IBs. Management of expected toxicities is described in Appendix C.

Toxicities related to cisplatin and docetaxel will be managed according to their respective USPI.

7.5 Adverse Events List

Most common adverse reactions (>20%) related to nivolumab alone were: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia.

The following hospitalizations are not considered SAEs in BMS supported clinical studies:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAES

7.6 Routine Adverse Event Reporting

Investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE version 4.0 is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.7 Routine Adverse Event Reporting to BMS

7.8 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. . All SAEs should be followed to resolution or stabilization.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The sponsor-investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

The sponsor-investigator will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to a The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

7.9 Expedited Adverse Event Reporting to Overall PI

Investigators **must** report to the

Investigators will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy, using the local institutional SAE form.

7.10 DF/HCC Expedited Reporting Guidelines

For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

	DF/HCC Reportable AEs					
Attribution	**Gr. 1 AE Unexpected**	**Gr. 1 & 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated / Unlikely	Not required	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible / Probable / Definite	Not required	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*

If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 hours of learning of the event.

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.11 Expedited Adverse Event Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria below for expedited reporting:

Any unexpected fatal or life-threatening suspected adverse reactions should be reported no later than 7 calendar days after initial receipt of the information. Address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

7.12 Expedited Adverse Event Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.13 Expedited Adverse Event Reporting to BMS

SAEs, whether related or not related to study drug, and pregnancies must be reported

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.

8.1 IND Agent Nivolumab

8.1.1 Description

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. A description of the physical and chemical properties of nivolumab are provided below.

Product Description 1	
BMS Number	**BMS-936558-01 or BMS-936558**
Other Names	Opdivo®, nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	10 mL vial	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing

8.1.2 Storage and Stability

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to section 5 of this protocol.

8.1.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.4 Availability

8.1.5 Ordering

Pharmacies at all participating sites will request supply of nivolumab, directly from Bristol-Myers Squibb, by submitting an order form, provided by Bristol-Myers Squibb.

8.1.6 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.7 Destruction and Return

Unused supplies and expired supplies of the investigational agents will be destroyed on site, by the pharmacy, per institutional SOP.

8.2 Other Agents

TPN regimen will be stored, prepared, and administered per standard of care/institutional standard.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies are planned as part of this study.

9.1 Biomarker Studies

Biopsy confirmed squamous cell carcinoma of the larynx or hypopharynx is a requirement to be enrolled on this study.

Tumor biopsies and/or surgery should not generally be performed on Friday afternoons, as there may not be time for If a biopsy or surgical resection is performed , of the Belfer Center for Applied Cancer Science should be notified ahead of time to ensure that there will be adequate time for processing fresh tissue or serum samples, since these should not be stored over the weekend.

Each tumor and blood sample obtained will be assigned a unique coded identifier in order to preserve the confidentiality of the participant. The coded samples will be linkable to the participant, but the key that links that person to the unique identifier will be stored in a database housed on a server at the DFCI. Access to participant identity will be provided only to the principal investigator and study staff (not laboratory staff). There are multiple firewalls and passwords protecting the data from unwanted viewers. Patient privacy will be maintained by strictly curtailing access to the electronic file via passwords and firewalls. The coded samples will be cryopreserved and stored in secure locked freezers. Once all research is complete, the link between the coded samples and patient identifiers will be destroyed.

If only an archival pre-treatment biopsy sample is obtained, the formalin-fixed paraffin-embedded (FFPE) tissue block should be obtained for research sample allocation. Preparation from the BWH Specialized Histopathology Core for genomic sequencing and we will request preparation of

If a

At the time of each blood sample collection (see *Study calendar*), 2 tubes are requested:

Multiparametric flow cytometry

Immunohistochemistry

Genomic sequencing

10. STUDY CALENDAR

Screening evaluations are to be conducted within 3 weeks prior to study registration. Procedures done within a week of study registration don't need to be repeated to establish baseline. Scans must be done Laboratory evaluations do not need to be repeated to meet eligibility criteria In an event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. TPN cycle will be 21 days long, and subsequent nivolumab cycles will be 28 days long.

Assessments must be performed prior to administration of any study agent.
unless otherwise noted.

Informed consent	X													
Medical History	X													
Concomitant Medicines	X													
HPV Testing[A]	X													
Physical exam (Ht, Wt, VS, PS)[B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine labs[C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-HCG (WOCBP only)[D]	X				X									X
ECG	X													X
Radiologic evaluation[E]	X			X[F]										X[E]
Biopsy sample[G,H]	X													
Correlative blood	X	X		X	X			X					X	X
TPN (docetaxel, cisplatin, nivolumab)[I]		X	X	X[J]										
Nivolumab					X[K]		X		X		X[L]	X[M]		
IMRT[N]					X	X	X	X	X	X	X			
Quality of life survey[O]	X				X							X	X	X
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X

a) Patients must have HPV negative disease. Those patients with a supraglottic primary are required to undergo HPV testing with p16 immunohistochemistry and/or confirmatory HPV PCR or ISH testing to rule out oropharyngeal origin with laryngeal extension
b) Physical exam is symptom directed. Height measured at screening only.
c) Routine labs include: CBC with diff, LFTs, CMP, Mg, TSH. Baseline HCV antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody testing is required. TSH (and free T4 if TSH is abnormal) is required less frequently according to the following schedule:

d) Serum or urine within 24 hours prior to first dose of induction TPN.
e)

f) Subjects will undergo repeat neck CT or MRI or PET-CT following the completion of the induction phase of treatment (at least 10 days after the completion of the last TPN infusion).
g)
h) Fresh biopsy is mandatory (if safe to perform) if archival tissue is not available. FNA cytologic samples are not permitted.
i) Patients will receive oral levofloxacin 500 mg daily by mouth on D5-15 of the cycle for antibiotic prophylaxis. In addition, granulocyte-colony stimulating factor (GCSF) support can be administered (at the treating physician's discretion) at least 24 hours (but no later than 72 hours) after completion of the TPN infusion in the form of pegfilgastrim 6 mg subcutaneously once or as tbo-filgastrim administered subcutaneously daily at least 24 hours after the completion of the TPN infusion (but no later than 72 hours). Tbo-filgastrim should be given for at least 5 days and continued for a maximum of 14 days or until the ANC is at or above 1000. Tbo-filgrastim should not be given with 24 hours of the start of the next cycle of TPN. Standard pre-medications including dexamethasone, palonosetron or ondansetron, and fosaprepitant are permitted for anti-emetic effect. Pre-medication with dexamethasone prior to taxane exposure is permitted and strongly encouraged.
j) Of note,

k) Nivolumab will start concurrently with IMRT and is repeated every 14 days or 2 weeks during IMRT. If individual RT fractions are canceled or delayed at the discretion of the treating radiation oncologist, nivolumab can be continued on a 2 week schedule to overlap with RT until the completion of radiation.
l) Administration of the final dose of nivolumab is permitted +/- 5 days from the last fraction of IMRT.
m) Adjuvant nivolumab should begin within 3-8 weeks following the completion of nivolumab + IMRT (from the last day of RT). Nivolumab will then be dosed every 28 days (4 weeks per cycle) for up to 6 months (or 6 cycles).
n) IMRT (intensity modulated radiotherapy) begins at least 21 days or 3 weeks after the completion of the last cycle of TPN and after restaging scans. The first fraction of RT should be administered no later than 6 weeks (or 42 days) after the last cycle of TPN begins.
o) Quality of life surveys will be completed at screening, after completion of induction TPN and nivolumab-IMRT, at the end of adjuvant nivolumab treatment, and at 30-day follow-up. Patients will complete the EORTC QOL Module for Head and Neck Cancer (QLQ-C30 and HN35). See Appendix D for the full questionnaires.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants

following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 of induction TPN will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a
representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol

and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for

independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	
PD	Any	Yes or No	PD	
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. **
Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Time-to-event Endpoint Definitions

Laryngectomy-Free survival: defined as time from study registration to earlier of surgical removal of larynx and/or hypopharynx, or death due to any cause. Participants alive with intact larynx and hypopharynx are censored at date of last disease evaluation.

Laryngo-Esophageal Dysfunction-Free Survival: defined as time from study registration to earlier of surgical removal of larynx and/or hypopharynx, non-functioning larynx and/or hypopharynx (inability to swallow, speak, and/or breath on own), or death from any cause. Participants alive

with intact and functioning larynx and hypopharynx and esophagus are censored at date of last disease evaluation.

Disease-free survival: defined as time from study registration to earlier of removal of larynx/hypopharynx (i.e. local/locoregional recurrence), distant disease recurrence, invasive second primary, or death due to any cause. Participants alive without one of these events are censored at date last know event-free.

Overall Survival: Overall Survival (OS) is defined as the time from study registration to death due to any cause, otherwise, participants are censored at date last known alive.

11.1.7 Quality of life Assessment

Quality of Life Assessment: The EORTC QOL Module for Head and Neck Cancer (QLQ-C30 and HN35, *see Appendix D*) will be used to assess the effect of cancer treatment on physical, social and emotional well-being and function. The survey consists of 30 and 35 items, respectively.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention

for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

This is a one arm phase II trial.

The primary efficacy population includes all eligible patients who begin protocol treatment(the evaluable population).

Adverse events will be classified and graded according to the CTCAE v.4.0. and frequencies will be summarized among patients who begin protocol therapy.

In addition to the continuous routine toxicity monitoring by the study team throughout the duration of the trial, the following

These events and rates will be continuously monitored and decisions made regarding the overall status of the trial.

For the primary endpoint, the Kaplan-Meier method will be used to estimate LFS. For other secondary objectives: Best overall response will be summarized

Another endpoint is to assess quality of life (QOL

14. PUBLICATION PLAN

The results should be made public

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