

Mayo Clinic Cancer Center

**Phase 2 study of Pembrolizumab Combined with Chemoradiation Therapy
in Anaplastic Thyroid Cancer**

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Drug Company Supplied: Pembrolizumab (MK-3475) IND 135041 (EXEMPT)

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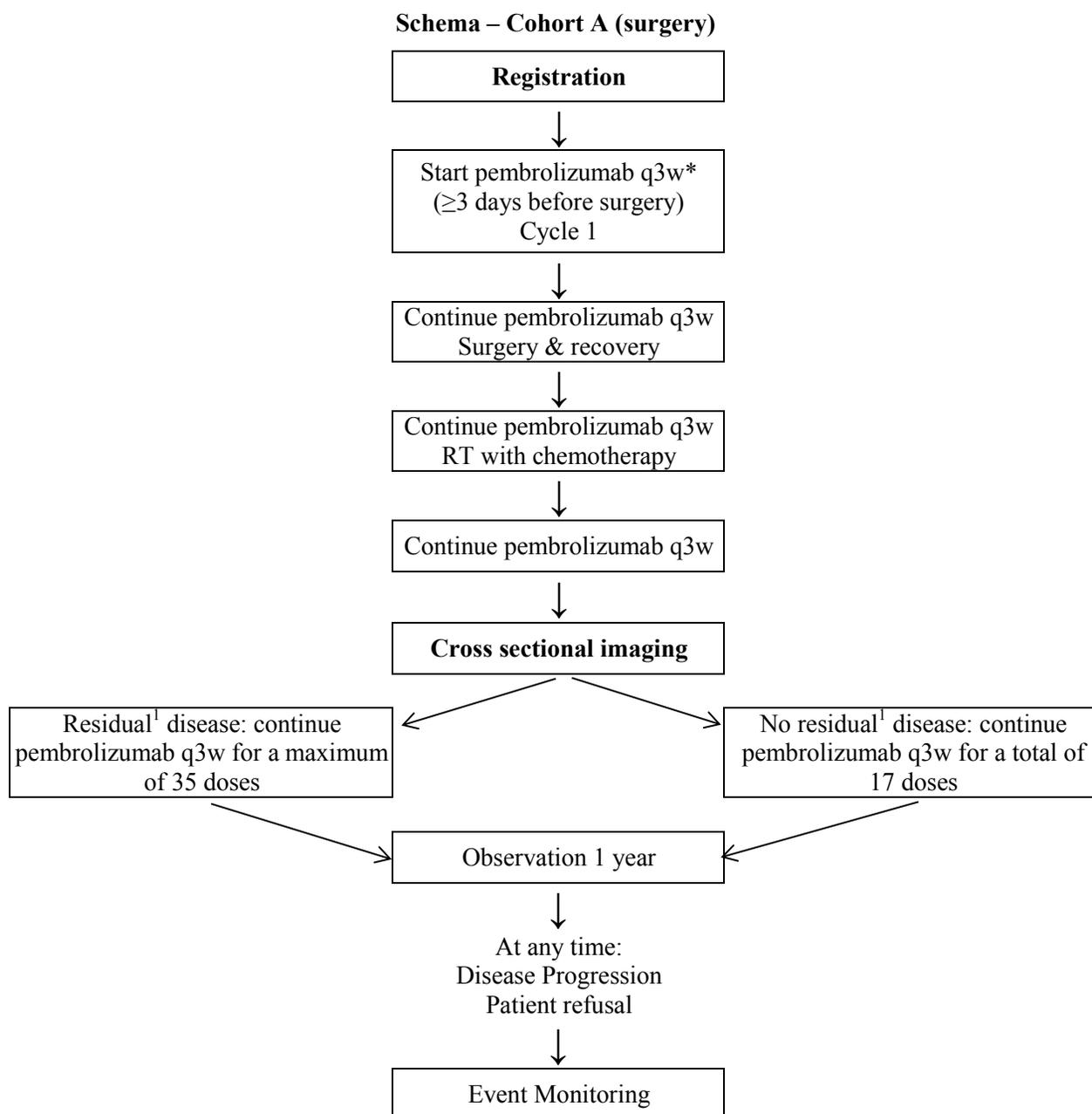
Protocol Resources

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*No waivers of eligibility allowed

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*Cycle = 21 days

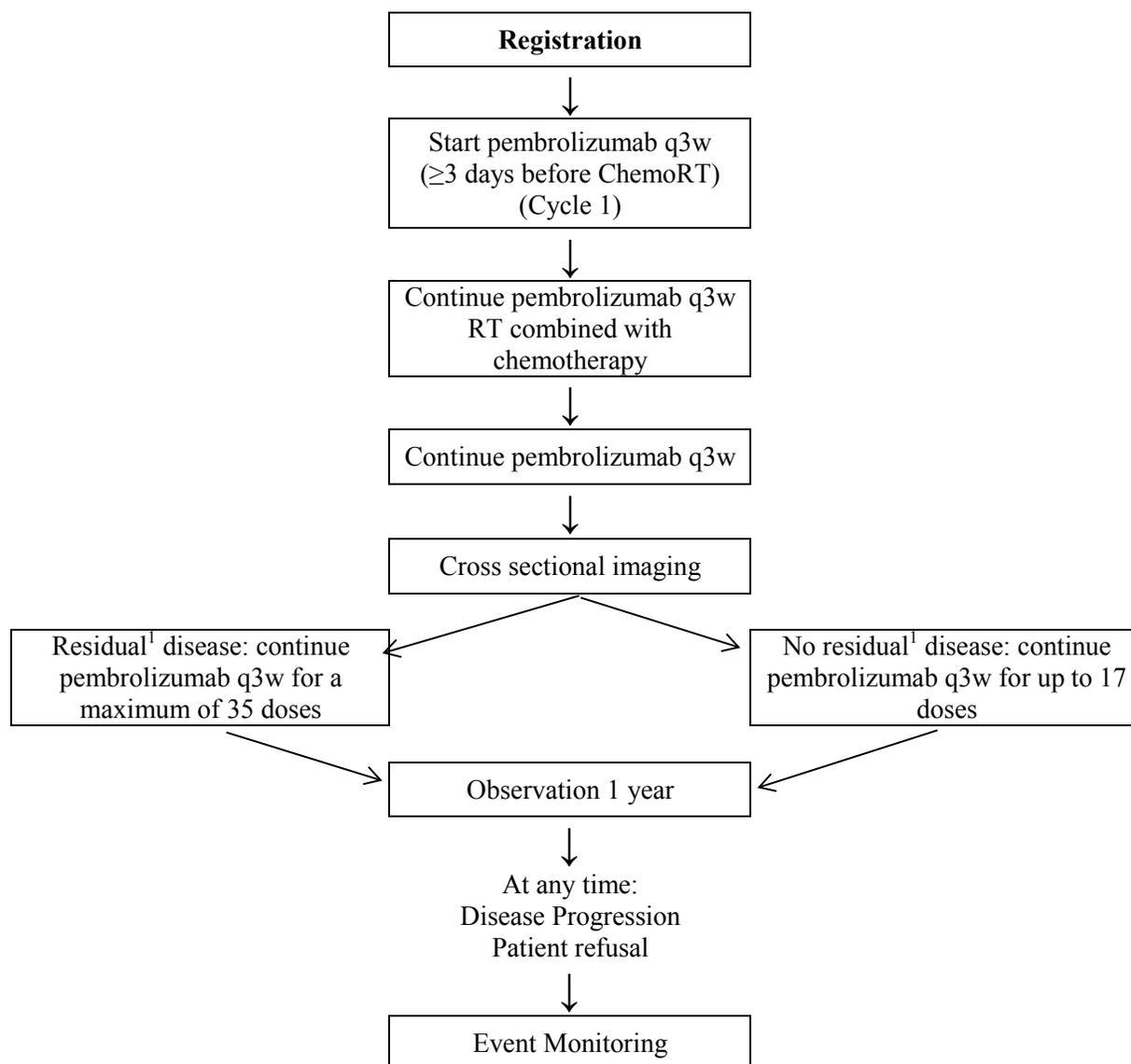
NOTE: all cycles will be based on pembrolizumab given once every three weeks.

Surgery, chemo and radiation therapy may be given as clinically indicated and any delays are per healthcare provider's discretion. They do not affect the cycle length. (See [Section 7.1](#))

¹Residual disease is defined in [Section 11.33](#)

Generic name: Pembrolizumab (MK-3475) Brand name(s): Keytruda® Mayo Abbreviation: MK3475 Availability: Mayo Clinic Pharmacy	Generic name: Docetaxel Brand name(s): Taxotere, Docefrez Mayo Abbreviation: TATER Availability: Commercial	Generic name: Doxorubicin Brand name(s): Adriamycin Mayo Abbreviation: ADR Availability: Commercial
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Schema – Cohort B (no surgery)



*Cycle = 21 days

NOTE: All cycles will be based on pembrolizumab given once every three weeks.

Surgery, chemo and radiation therapy may be given as clinically indicated and any delays are per healthcare provider’s discretion. They do not affect the cycle length. (See [Section 7.1](#))

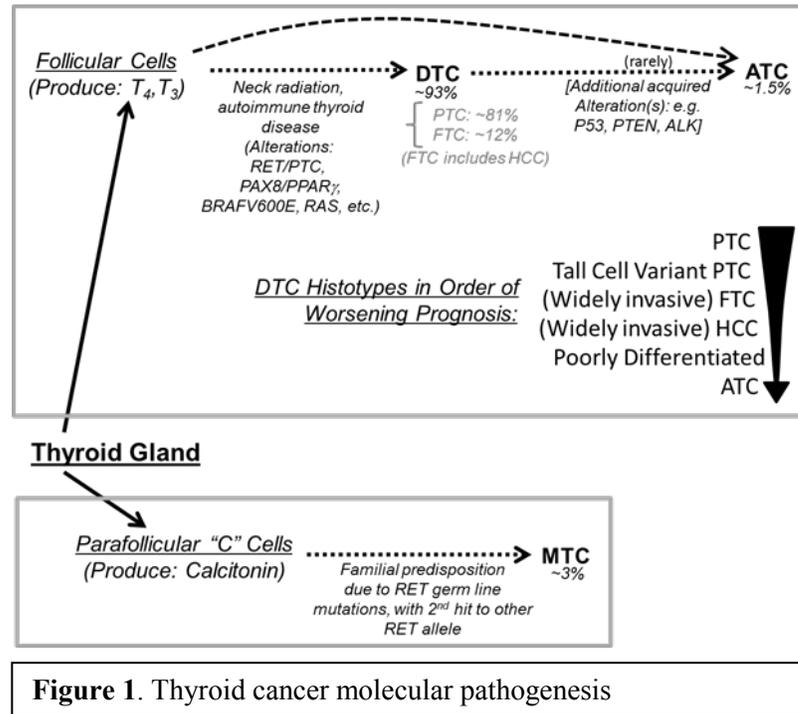
¹Residual disease is defined in [Section 11.33](#)

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1.0 Background

1.1 Thyroid Cancer Overview

Thyroid cancer incidence is rising more rapidly than for any other cancer. Thyroid cancers include differentiated thyroid cancers (DTC, including papillary and follicular variants), medullary thyroid cancer and a highly aggressive variant, undifferentiated or anaplastic thyroid cancer (ATC; **Figure 1**) (Bible and Ryder 2016).



ATC is perhaps the most aggressive human cancer. Historically, fewer than 20% survive 1 year, median overall survival is ~5 months, and it is almost universally fatal (McIver, Hay et al. 2001; Goutsouliak and Hay 2005; Albores-Saavedra, Henson et al. 2007; Dandekar, Harmer et al. 2009; Bible, Suman et al. 2012; Mohebbati, Dilorenzo et al. 2014). Doxorubicin is the only FDA approved medication for this malignancy, but has poor efficacy [~5% ORR in a randomized study (Shimaoka, Schoenfeld et al. 1985)]. Multimodality therapy combining surgery, radiotherapy and cytotoxic chemotherapy appears to produce improved survival, but all ATC patients are ultimately expected to succumb to their disease, mostly from distant metastatic disease (Bible et al., unpublished data, see [Section 1.2](#) and [Section 1.5](#) and **Figure 5**). More effective therapies are sorely needed.

1.2 Current treatment strategies for Anaplastic Thyroid cancer

Treatment for ATC is an oncologic emergency as tumor doubling time can sometimes only be in days. Treatment should be instituted expeditiously, and requires input from an experienced multidisciplinary team, ideally undertaken at high volume centers. ATC is highly aggressive and is highly invasive into neighboring anatomical structures such as esophagus and trachea, and therefore represent an emergent threat to airway and to esophagus, as well as to vessels and nerves.

Surgical resection is technically difficult in almost all ATC cases. However, there is evidence from several retrospective studies that surgical resection may improve survival in ATC patients (De Crevoisier, Baudin et al. 2004; Akaishi, Sugino et al. 2011; Sugitani, Hasegawa et al. 2014; Kwon, Kim et al. 2016), and it has thus been our practice to aspire to resection if feasible. Due to morbidity, however, our practice is generally not to undertake laryngectomy, and instead settle for an R1 resection in cases in which para-laryngeal disease is prominent, as radiotherapy is uniformly administered in our practice after surgery in patients who elect an aggressive approach to their disease. This reflects a sense that the disease is often systemic and the goal is the rapid onset of chemotherapy and radiation therapy, which can be delayed by complex surgical wounds or wound complications.

Radiation therapy is an integral part of the treatment for ATC, both in the setting of curative intention and also as part of palliative treatment, even if best supportive care is otherwise elected. Multiple institutions over the years have reported their experience with multimodal therapy (Aldinger, Samaan et al. 1978; De Crevoisier, Baudin et al. 2004; Bhatia, Rao et al. 2010; Akaishi, Sugino et al. 2011; Foote, Molina et al. 2011; Mohebbati, Dilorenzo et al. 2014). It is unclear if accelerated or hyperfractionated radiation therapy incrementally improves outcomes (Heron, Karimpour et al. 2002; Dandekar, Harmer et al. 2009), but it has often been demonstrated from retrospective studies that radiation dose of >40-50 Gy is associated with better local control and overall survival (Akaishi, Sugino et al. 2011). Acute and late toxicity associated with radiation therapy for thyroid cancer includes painful mucositis requiring narcotic pain medications, thick secretions, altered taste, dehydration, malnutrition, laryngeal edema, cartilage necrosis, esophageal stenosis, xerostomia, and feeding tube dependence. Intensity modulated radiation therapy may be able to lessen the incidence and severity of these toxicities through lowering the daily dose and total dose to the oral cavity, pharyngeal, laryngeal and esophageal mucosa and major and minor salivary glands.

The most common chemotherapy regimens included in chemoradiation ATC studies included taxanes, doxorubicin and/or platinum agents.

Doxorubicin is the only FDA approved agent for the treatment of ATC and has been used with radiation

sensitizing agents in multiple studies (Aldinger, Samaan et al. 1978; Kim and Leeper 1983; De Crevoisier,

Baudin et al. 2004; Derbel, Limem et al. 2011; Foote, Molina et al. 2011; Sherman, Lim

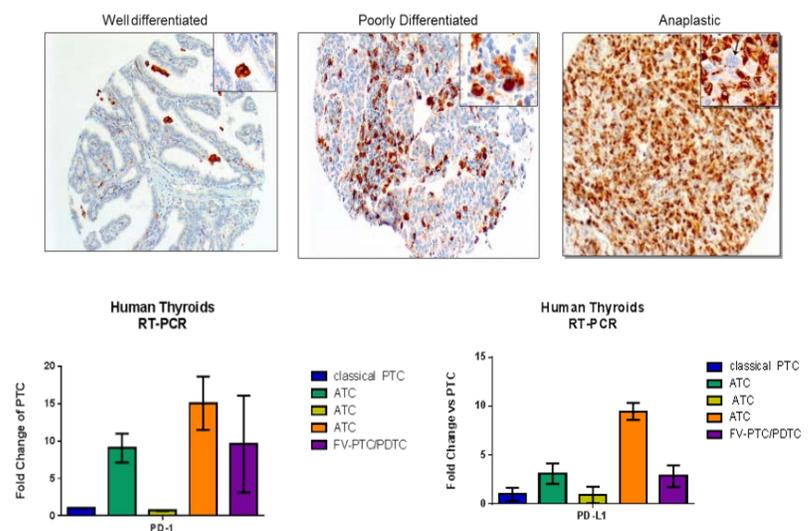


Figure 2. Tumor-associated macrophages in well-differentiated, poorly-differentiated and anaplastic thyroid cancer (top panel). Reverse-transcriptase polymerase chain reaction (RT-PCR) analysis of PD-1 and PDL-1 in thyroid cancer (bottom panel).

et al. 2011). Ain et al. demonstrated 53% ORR to paclitaxel in patients with persistent or metastatic ATC (Ain, Egorin et al. 2000), but duration of benefit was short. In recent studies, docetaxel has been also used in chemoradiation protocols for ATC, and has shown some promising efficacy (Troch, Koperek et al. 2010; Foote, Molina et al. 2011; Onoda, Kashiwagi et al. 2013; Onoda, Sugitani et al. 2015; Seto, Sugitani et al. 2015). Nevertheless, there is no defined standard of care chemotherapeutic agent or regimen to be used with radiation therapy. Use of a combination of these agents or any of these agents alone is reasonable, with current data favoring use of at least a taxane.

1.3 Immune microenvironment of Anaplastic Thyroid Cancer

Anaplastic thyroid cancers have a high expression of PD-1/PDL-1 (~70%), high mutational burden, ~45% rate of BRAF V600 mutation (which promotes a suppressive immune environment) and ~10% rate of microsatellite instability; in combination, all of these characteristics make ATC a prime target for immunotherapy.

- a. We have previously shown that nearly half of ATC tumor volume is composed of tumor-associated monocytes/macrophages (TAMs) (**Figure 2**) (Ryder, Ghossein et al. 2008; Ryder, Gild et al. 2013). Pre-clinical data in thyroid cancer mouse models demonstrate that TAMs promote tumor initiation and de-differentiation. Additionally, TAMs have potent immunosuppressive effects, particularly through influencing increased expression of PD-L1/PD-L2.
- b. Data from human tissues demonstrate increased gene expression of PD-1 and/or PD-L1 in aggressive thyroid cancers, including ATC (**Figure 2**) by RT_PCR.
- c. We have also demonstrated increased expression of PDL-1 by immunohistochemistry in approximately 80% of the human ATC samples available for testing. There was no PD-1 expression in these tumors as well as tumor stroma (**Figure 3**). Observed increased PDL-1 expression was demonstrated by others also (Bastman, Serracino et al. 2016), providing the rationale in the form of enhanced target expression for proposed pembrolizumab studies.

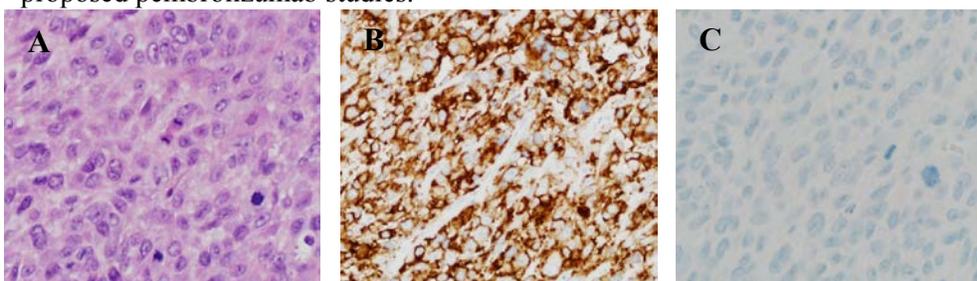


Figure 3. A. Hematoxylin-eosin stained section of ATC. B. Section of ATC showing diffuse positivity for PDL-1, and no staining for PD-1 (C).

- d. ATC shows high mutational burden with significant genetic alterations. In a recent study, ~70% of the ATC patients demonstrated P53 and TERT mutations (Landa, Ibrahimasic et al. 2016). In another study, similar findings were noted (Kunstman, Juhlin et al. 2015). Interestingly, both studies also demonstrated ~10% incidence of microsatellite instability (MSI_{high}) in ATC (Kunstman, Juhlin et al. 2015; Landa, Ibrahimasic et al. 2016). Both higher mutational burden and MSI_{high} status have been shown predictive of response to anti-PD-1 therapy in other cancers (Le, Uram et al. 2015; Rizvi, Hellmann et al. 2015).
- e. There is now also promising evidence that focal radiation therapy of solid primary or metastatic foci of disease, when combined with immune modulating therapies, can

induce potent tumor regressions in radiated and non-radiated foci of disease, the latter termed an **abscopal** effect. Multiple clinical trials are now ongoing to examine this combination strategy. Thus, in ATC patients, surgery/chemoradiation-induced increased expression of tumor-associated antigens, when coupled with PD-1 blocking antibodies, may have potential to induce potent and durable tumor responses as compared to chemoradiation alone.

- f. ATCs are associated with high incidence of BRAF mutations (~45%) (Landa, Ibrahimipasic et al. 2016). As in melanoma, mutant BRAF signaling is associated with the development of a suppressive immune tumor microenvironment, including through increased PD-1 expression (Angell, Lechner et al. 2014; Brauner, Gunda et al. 2016)
- g. Comprehensive immune phenotyping analyses of the blood of thyroid cancer patients, indicates alterations in circulating immune subtypes in advanced patients as compared to healthy volunteers and/or low risk disease patients (**Figure 4**). Such alterations in circulating immune phenotypes may reflect alterations at the level of the tumor microenvironment as well as predict responses to immune modulation. For example, patients with advanced, metastatic thyroid cancer have increased numbers of circulating CD8+/PD-1+ T cells as compared to healthy volunteers, suggesting an impaired anti-tumor immunity that may be reversible with PD-1 blocking antibodies.
- h. Further, ATC patients having received standard multimodal therapy with chemoradiation have the potential for increased expression of novel tumor-associated antigens, which, when coupled with PD-1 blocking antibodies, may be associated with potent tumor regression. This strategy is in fact the basis of several clinical trials in a variety of solid tumors.

Taken together, the data outlined above provide strong rationale to examine the efficacy of anti-PD-1 antibodies in patients with ATC, especially in combination with aggressive multimodal therapy.

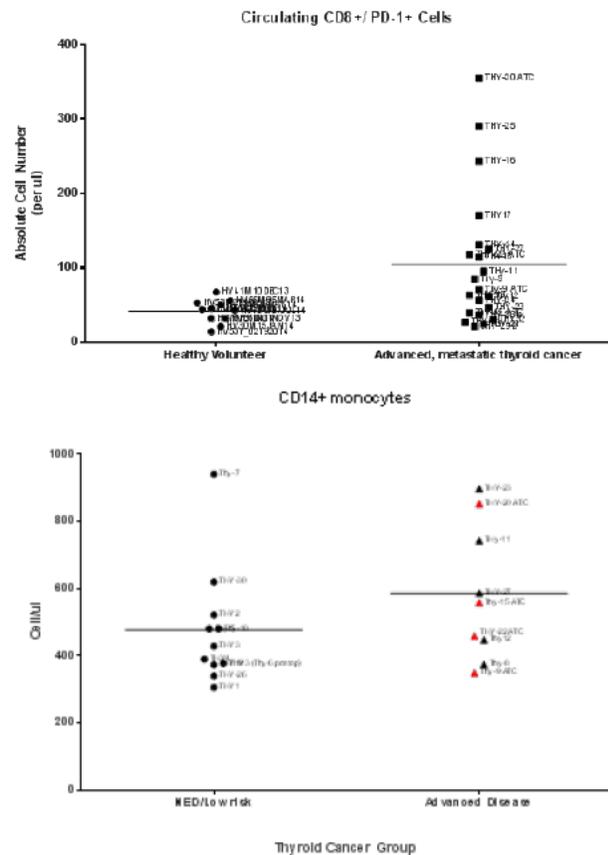


Figure 4. Circulating CD8+/PD1+ in healthy volunteers versus thyroid cancer patients (top panel) and CD14+ in low risk versus advanced thyroid cancer patients (bottom panel).

1.4 Pembrolizumab

Cancer cells are known to have the ability to evade immunosurveillance through a variety of mechanisms, including: reduced expression of tumor antigens, downregulation of MHC class I and II molecules for reduced tumor antigen presentation, secretion of immunosuppressive cytokines such as TGF-beta, recruitment or induction of immunosuppressive cells such as regulatory T cells (Treg) or myeloid derived suppressor cells (MDSC), and overexpression of certain ligands (eg, PD-L1) that inhibit the host's existing antitumor immunity (Tang, Wang et al. 2014). Recently, antibodies targeting the PD-1/PD-L1 or PD-L2 pathway have shown impressive and durable clinical benefit in melanoma, with promising activity emerging in multiple other solid tumors.

The programmed death 1 (PD-1) pathway is a negative feedback system that represses Th1 cytotoxic immune responses that, if unregulated, can damage the host (Nishimura, Nose et al. 1999; Nishimura, Okazaki et al. 2001; Chen 2004). It is up-regulated in many tumors and in their surrounding microenvironment. Blockade of this pathway with antibodies to PD-1 or its ligands has led to remarkable clinical responses in patients with many different types of cancer, including melanomas, non-small-cell lung cancer, renal cell carcinoma, bladder cancer, and Hodgkin's lymphoma (Brahmer, Tykodi et al. 2012; Topalian, Hodi et al. 2012; Hamid, Robert et al. 2013; Herbst, Soria et al. 2014; Powles, Eder et al. 2014; Topalian, Sznol et al. 2014; Ansell, Lesokhin et al. 2015). The expression of PD-1 ligands (PD-L1 or PD-L2) on the surface of tumor cells or immune cells is an important—but not a definitive—predictive biomarker of response to PD-1 blockade (Herbst, Soria et al. 2014; Powles, Eder et al. 2014; Taube, Klein et al. 2014; Topalian, Sznol et al. 2014; Ansell, Lesokhin et al. 2015).

Immunotherapeutic strategies aimed at overcoming immunotolerance and improving the activation of antitumor T cells represent a new promising therapeutic approach. Among them, pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In a phase I study, 655 patients with advanced melanoma were treated with pembrolizumab in four treatment cohorts using one of three dose schedules (10 mg/kg every two weeks, 10 mg/kg every three weeks, or 2 mg/kg every three weeks). Approximately three-fourths of patients had received prior systemic therapies for metastatic disease, including 52 percent who had received prior ipilimumab (Dua, Ribas et al. 2015). The overall objective response rate using RECIST criteria and central review was 33%. OS at 12 months was 66% and 49% at 24 months. Median PFS was 4.4 months, and 35% of patients remained progression-free at 12 months. On multivariate analysis, there were no significant differences in outcomes between the three dose schedules. Although these studies suggested that PD-L1 positivity correlated with increased responsiveness, absence of PD-L1 expression did not preclude a clinical response. Treatment-related toxicities were manageable; 83 percent of patients experienced one or more treatment-related adverse events. The most common toxicities were fatigue, pruritus, rash, diarrhea, and arthralgia (36%, 24%, 20%, 16%, and 16%, respectively). Overall 14% of patients experienced Grade 3 or 4 toxicities, the most common being fatigue (2%), and there were no treatment-related deaths.

Two phase III studies, first with ipilimumab-refractory advanced melanoma patients who were randomly assigned to pembrolizumab (2 mg/kg every three weeks), pembrolizumab (10 mg/kg every three weeks) or chemotherapy (carboplatin plus paclitaxel, paclitaxel alone, dacarbazine, or temozolomide per institutional standard) (Ribas, Puzanov et al. 2015); and second, where pembrolizumab 2 mg/kg and 10 mg/kg doses were compared with ipilimumab (Robert, Schachter et al. 2015) in ipilimumab-naïve patients; resulted in

US Food and Drug Administration (FDA) approval of pembrolizumab at a dose of 2 mg/kg every three weeks in September 2014.

The safety and efficacy of pembrolizumab monotherapy was recently assessed in patients with advanced non-small-cell lung cancer (NSCLC) (Garon, Rizvi et al. 2015). Common side effects attributed to pembrolizumab were fatigue, pruritus, and decreased appetite. Among all patients, ORR was 19.4%, and the median duration of response (DOR) was 12.5 months.

Pembrolizumab has since been shown to be efficacious in many solid tumors including, head and neck cancer. KEYNOTE-012, a phase 1b trial with recurrent and metastatic head and neck cancers, studied the role of single agent pembrolizumab. Only patients who were PD-L1+ were enrolled, but later an expansion cohort allowed PD-L1- patients to enroll. One hundred and four patients were screened and 60 patients with PD-L1-positive squamous cell carcinoma of the head and neck were enrolled and treated: 23 (38%) were HPV-positive and 37 (62%) were HPV-negative. Overall response by central imaging review was 18% (eight of 45 patients; 95% CI 8–32) in all patients, and was 25% (four of 16 patients; 7–52) in HPV-positive patients and 14% (four of 29 patients; 4–32) in HPV-negative patients (Seiwert, Burtness et al. 2016). Similar results were seen for efficacy in the expansion cohort. Another phase 2 study, KEYNOTE-055, enrolled recurrent and metastatic head and neck squamous cell carcinoma patients who had failed platinum and cetuximab therapy. This study screened 228 patients and enrolled 172. Eighty-four percent of the patients had ≥ 2 lines of therapy and 41% were HPV-positive. Again, treatment was well tolerated, and 12% of patients demonstrated grade ≥ 3 adverse events. Overall response rate (ORR) was 22% in patients who had at least 6 months of follow up (Bauml, Seiwert et al. 2016).

Keytruda™ (pembrolizumab) has been approved in the United States for the treatment of {per Keytruda® (pembrolizumab) package insert 2016}:

- Patients with unresectable or metastatic melanoma
- Patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) $\geq 50\%$)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC
- Patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA
- Patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy

1.5 Multimodal treatment (Mayo Clinic) protocol for treatment of ATC

As mentioned above, ATC is undifferentiated carcinoma of the thyroid gland that is rare (<2% of all thyroid cancers), has historically dire prognosis, and is almost universally fatal (Albores-Saavedra, Henson et al. 2007; Bible and Ryder 2016), leading to a disproportionately high fraction of thyroid cancer-related deaths (Are and Shaha 2006; Neff, Farrar et al. 2008). Randomized clinical trials have seldom been initiated in ATC. The combination of rarity of the diagnosis and extremely limited median survival of 4-6 months, has made it difficult to accrue to randomized clinical trials (McIver, Hay et al. 2001; Goutsouliak and Hay 2005; Sherman, Lim et al. 2011; Mohebbati, Dilenzo et al.

2014). Therefore, to date, doxorubicin, with its very limited efficacy, is the only FDA-approved agent for the treatment of this malignancy. New treatment strategies and agents are sorely needed – but highly challenging to develop and pilot.

In the absence of currently available randomized data, and considering impediments in obtaining such data in the near future, we, at the Mayo Clinic initiated an aggressive combined-modality treatment strategy offered to a selective, consecutively treated cohort of ATC patients at our institution. We hypothesized that implementation of practice change, embracing more uniform and aggressive multimodal therapy (MMT; including surgery, combination chemotherapy and intensity modulated radiation therapy) as feasible, might lead to improved survival. We carefully select patients for this treatment protocol after a thorough multidisciplinary assessment with input from medical oncology, radiation oncology and otorhinolaryngology. Consenting patients who are fit, have no stage IVC disease, and are expected to have negative margins after resection of the thyroid mass, undergo surgery. Combination chemotherapy, preferably weekly dosing, is initiated as soon as the patient has convalesced from surgery, or immediately if surgery is not planned. Radiation therapy with intensity modulated radiation therapy (IMRT) is initiated after careful review and planning by radiation oncologists either as an adjuvant or primary therapy. This therapy obviously has its usual expected toxicities such as mucositis, dysphagia, pain, nausea, vomiting, weight loss, cytopenias, and neutropenic fever. Nearly half of the patients undergo feeding tube placement and require hospitalization for complications related to dehydration, mucositis, and pain control. However, the protocol is usually completed with close monitoring and initiation of mitigating measures promptly for toxicities.

We have previously published the outcomes of 10 consecutively treated stage IVA and IVB ATC patients from our institution and demonstrated that with aggressive combined modality treatment median OS was dramatically improved when compared to an historical cohort of patients treated at our institution in the preceding 50 years (60 months versus 5-6 months)(McIver, Hay et al. 2001; Foote, Molina et al. 2011). We have continued to use this MMT approach and have now treated 30 patients with this method. Eighteen (18) were treated with best supportive care using a short course of palliative radiation (palliative group). We completed the MMT in most patients. In the MMT cohort, surgery and chemoradiation therapy was administered to 27 (90%) and 30 (100%) patients respectively. Twenty (70%) patients received $\geq 80\%$ of planned chemotherapy doses during radiation therapy.

Median overall survival (OS) was 21 months, and 1 year survival was 57% (95% CI, 39-74; **Figure 5A**). However, it appears that this approach has not improved the survival of stage IVC patients. OS of stage IVC patients did not differ in MMT versus the palliative cohort (HR, 1.15, 0.4-3.2; P=0.78; **Figure 5B**). The majority of the patients, including the MMT cohort, ultimately died of distant disease. In the MMT cohort, 2 of 27 (7%) patients had locoregional relapse and 21 of 27 (77%) had new distant metastasis or progression of distant metastasis on follow up.

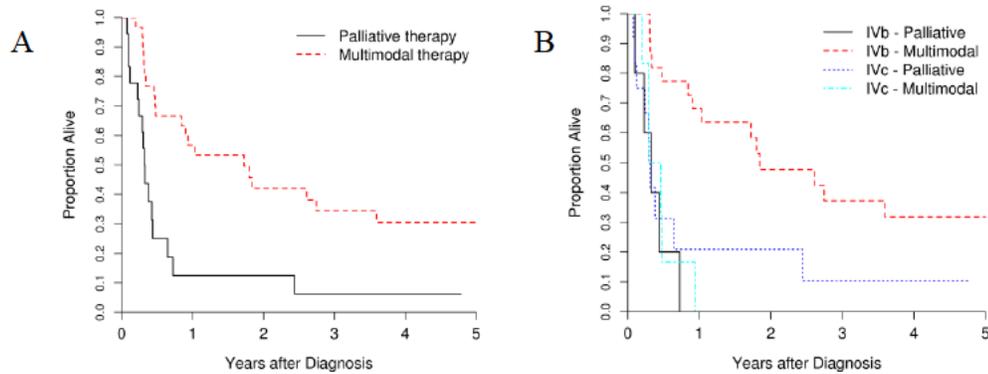


Figure 5. Overall survival (A) and progression-free survival (B) in ATC patients treated with multimodal therapy and palliative treatment at the Mayo Clinic, Rochester from 2003-2015.

However, there is great need of prospective studies incorporating an MMT approach and novel agents to better control micrometastatic disease that is most commonly fatal.

1.6 Combining pembrolizumab with chemoradiotherapy

The adverse events associated with pembrolizumab are mostly Grade 1-2. Severe grade ≥ 3 adverse events were immunologic in origin and related to the lungs, lower gastrointestinal tract, skin, and liver. Adverse events related to chemoradiation therapy include mucositis, dysphagia, pain, thickened saliva, loss of taste, weight loss, cytopenias, and neutropenic fever. These events do not overlap with the adverse events from pembrolizumab. Pembrolizumab following chemoradiation has been found to be safe in lung cancer (Durm, Kio et al. 2016). There were no Grade 4 or 5 toxicities and no cases of esophagitis were noted (radiation recall).

There are number of ongoing trials where immunotherapy with anti-PD-1 agents is being combined with chemoradiation, including head and neck squamous cell carcinomas (NCT02586207, NCT02759575, NCT02819752, NCT02764593). Pembrolizumab is also now being investigated for its safety and efficacy with radiation therapy in the adjuvant setting (NCT02641093) and prior to surgery (NCT02296684) in a window-of-opportunity trial for locally advanced head and neck carcinomas. The chemoradiation therapy used for head and neck squamous cell carcinomas is very similar in terms of toxicity relative to the chemoradiation protocol used for ATC.

1.7 Rationale for this study

- As described above, ATC is highly lethal cancer with possibility of rapid death if left untreated and has no effective standard of care therapies.
- Our combination multimodal treatment platform involving surgery, chemotherapy and radiation likely increases survival in highly selected patients. Despite this small success, the majority of patients ultimately develop distant metastases, and succumb to their disease.
- ATC, pursuant to the current preclinical data described above in [Section 1.3](#), provides an attractive target for immunotherapy.
- Chemoradiation therapy with or without surgery additionally has potential to uncover tumor antigen facilitating breakdown of immune tolerance, providing a highly attractive platform for the addition of superimposed immunotherapeutic approaches.

Thus, we hypothesize that a multimodal therapy protocol involving surgery, chemotherapy, and radiation therapy coupled with immunotherapy with an anti-PD1 agent such as pembrolizumab will decrease the incidence of distant metastasis in this disease thus improving survival outcomes.

1.8 Rationale for correlative studies

1.81 Immune phenotyping the peripheral blood

As not all patients respond to immunotherapeutic approaches, there is considerable importance for the elucidation of pre-and on-going therapy biomarkers that predict therapeutic responses. Tumor-driven alterations in the phenotype and/or trafficking of immune subtypes from the periphery and into tumors may be identified by examining the peripheral blood of cancer patients (Gustafson, Lin et al. 2014). Comprehensive multi-color FACS analyses of whole blood using an established and published protocol has identified distinct immune profiles from a broad spectrum of cancer patients that may be unique or shared across cancer types, are distinct from healthy controls, and predict outcomes. For example, immune phenotyping suggests that a higher ratio of CD4⁺ T cells to CD14⁺HLA^{lo/neg} monocytes (putative MDSC) in peripheral blood independently predicts prolonged survival in cancer patients (Gustafson, Lin et al. 2015). Furthermore, increased concentration of peripheral blood CD14⁺HLA^{lo/neg} monocytes may hinder the generation of activated, mature DCs in DC vaccine protocols, perhaps contributing to mixed responses in DC vaccine trials (Laborde, Lin et al. 2014). Thus, the state of host immunity and the ability to induce anti-tumor responses is a critical component for immune checkpoint inhibitors. We hypothesize that dynamic immune phenotyping pre- and post chemoradiation (combined with pembrolizumab) will serve as a biomarker for immune-driven alterations in the tumor that can be used to identify responders and/or to identify cell types associated with resistance that can be used to develop improved combination immune base strategies to improve overall response rates.

1.82 Response evaluations using cytokines, genetics and antithyroid antibodies

As noted above, there is a strong need to identify potential biomarkers for responses to immune-based therapeutics as well as understand toxicities or immune-related adverse effects (irAEs) following immune based therapies. Analyses of cytokine alternations pre-and post pembrolizumab in the serum may reflect relevant immune-related alterations at the tumor site as well as systemically. These profiles may be used to better predict patients likely to respond to on-going pembrolizumab infusions as well as at risk for potential irAEs that may be minimized with early interventions.

Thyroid autoantibody screens: ATCs often develop from differentiated thyroid cancers (DTC), the latter of which are often associated, at least initially, with clinical and/or subclinical autoimmune thyroid disease (i.e. an anti-thyroid response). In DTCs co-existent with autoimmune thyroid disease, overall outcomes are reportedly favorable from limited studies, suggesting the presence of an intact anti-tumor immune response. As DTCs progress, however, to PDTC and ATCs, tumors become heavily infiltrated with TAMs that, together with acquired intrinsic tumor cell genetic alterations, promote an immunosuppressive tumor environment and tumor escape from host-mediated anti-tumor control. We hypothesize that development of anti-thyroid antibodies could predict the responders from non-responders when treated with pembrolizumab.

BRAF, P53 and TERT mutations are common in ATC and likely contribute to the pathogenicity (Liu, Bishop et al. 2016). Molecular alterations within the ATCs may also identify molecular pathways associated with response and/or resistance to pembrolizumab (Brauner, Gunda et al. 2016). This may allow future studies where they could be targeted to improve anti-PD-1 response and overcome resistance. We will therefore interrogate if these somatic mutations are associated with the proposed outcomes in a prospective fashion.

1.83 Circulating Tumor Cells (CTCs)

The load and decrease in CTC numbers have been shown to be prognostic markers in many cancers including breast (Cristofanilli, Budd et al. 2004; Liu, Shields et al. 2009; Smerage, Barlow et al. 2014) and thyroid cancer (Xu, Handy et al. 2016). However, data from ATC is lacking and we will aim to prospectively collect circulating tumor cells and correlate with outcomes. The RareCyte CTC technology is a comprehensive, reproducible and highly sensitive dual-platform for collecting, identifying and analyzing CTCs that does not rely on EpCAM expression for enrichment. (Campton, Ramirez et al. 2015). This platform allows for mechanically precise CTC retrieval, enabling the isolation of DNA derived from single or pooled CTCs for advanced genomic analyses including the detection of specific mutations and targeted NGS.

2.0 Objectives

2.1 Primary objective

To assess the efficacy of pembrolizumab in improving overall survival at 6 months (OS-6) in combination with multimodal therapy involving standard chemo-radiotherapy in ATC in comparison to an historical cohort.

2.2 Secondary Objective

To determine safety and tolerance of pembrolizumab with chemoradiotherapy.

2.3 Exploratory Objectives

2.31 To evaluate locoregional control

2.32 To evaluate progression of distant metastases

2.4 Correlative Research

2.41 To evaluate the evolution of the immune profile of circulating immune cells in response to therapy in ATC patents, and to assess potential correlations with outcomes on an exploratory basis.

2.42 To evaluate PD-1 and PD-L1 staining in tumor cells and tumor stroma as candidate biomarkers for outcomes.

2.43 To determine if pre-therapy circulating tumor cell load is associated with outcomes.

2.44 To examine associations between outcomes and somatic mutational status as assessed by foundation medicine analysis (for example: presence of BRAF, RAS, P53 and TERT promoter mutations).

3.0 Registration Patient Eligibility

3.1 Registration – Inclusion Criteria

- 3.11 Age ≥ 18 years.
- 3.12 Histological confirmation of, or cytology reported and confirmed, anaplastic thyroid cancer in thyroid mass and/or regional lymph nodes.
NOTE: A diagnosis reported as “poorly differentiated carcinoma consistent with anaplastic thyroid cancer” will be accepted.
- 3.13 Prior neck radiotherapy that would preclude re-irradiation.
- 3.14 ECOG Performance Status (PS) 0 or 1 ([Appendix I](#)).
- 3.15 The following laboratory values obtained ≤ 14 days prior to registration:
- Hemoglobin ≥ 9.0 g/dL
 - Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Total bilirubin $\leq 1.5 \times \text{ULN}$ (except for patients with well-documented Gilbert’s Syndrome)
 - Aspartate transaminase (AST) $\leq 3 \times \text{ULN}$
 - Creatinine $\leq 1.5 \times \text{ULN}$
- OR
- Calculated creatinine clearance ≥ 50 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

- 3.16 PT/activated PTT $\leq 1.5 \times \text{ULN}$, unless subject is receiving anticoagulant therapy and PT or aPTT is within therapeutic range of intended use of anticoagulants.
- 3.17 Negative pregnancy test done ≤ 7 days prior to registration, for persons of childbearing potential only.
NOTE: If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
NOTE: Merck requires an additional pregnancy test if eligibility pregnancy test is >72 hours prior to first dose.
- 3.18 Persons of childbearing potential must be willing to use an adequate method of birth control (as outlined in [Section 9.9c](#)) for the course of the study through 120 days after the last dose of study medication.
NOTE: Abstinence is acceptable if this is the usual lifestyle and preferred method of contraception for the patient.
- 3.19a Persons able to father a child must agree to use an adequate method of contraception (as outlined in [Section 9.9c](#)) starting with the first dose of study therapy through 120 days after the last dose of study therapy.
NOTE: Abstinence is acceptable if this is the usual lifestyle and preferred method of contraception for the patient.

- 3.19b Provide written informed consent.
- 3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).
- 3.19d Willing to provide tissue and blood samples for correlative research purposes
- 3.2 Registration – Exclusion Criteria
- 3.21 History of non-infectious pneumonitis that required steroids or current pneumonitis.
- 3.22 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant persons
 - Nursing persons
 - Persons of childbearing potential who are unwilling to employ adequate contraception
- 3.23 Any autoimmune disease such as inflammatory bowel disease, including ***but not limited to:***
- Ulcerative colitis
 - Crohn’s Disease
 - Rheumatoid arthritis
 - Systemic sclerosis
 - Systemic lupus erythematosus
 - Autoimmune hepatitis
 - Other autoimmune disease not listed above
- NOTE: Subjects with autoimmune thyroid disease and diabetes mellitus type I will be allowed.
- 3.24 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.
- 3.25 Other active malignancy ≤ 6 months prior to registration.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix or or prostate cancer confined to prostate gland or coexistent differentiated thyroid cancer.
NOTE: If there is a history of prior malignancy, they must not be receiving other treatment for their cancer.
Ongoing adjuvant hormonal treatment for breast cancer is allowed.
- 3.26 Prior known allergic reaction to pembrolizumab or its excipients.
- 3.27 Untreated brain metastasis.
- 3.28 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.

- 3.29a Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.
- 3.29b Received any live vaccine ≤ 30 days prior to registration
- 3.29c Any of the following conditions ≤ 6 weeks prior to registration:
- Cerebrovascular accident (CVA)
 - Admission for unstable angina
 - Cardiac angioplasty or stenting or coronary artery bypass graft surgery
 - Untreated pulmonary embolism or untreated deep venous thrombosis (DVT)
 - Arterial thrombosis
 - Class III or IV heart failure as defined by the NYHA functional classification system ([Appendix II](#))

4.0 Test Schedule

4.1 ATC Test Schedule - Cohort A with Surgery

Tests and procedures ¹	Window	Active Monitoring Phase						
		≤14 days prior to registration	Pembro (Cycle 1) ²	Pembro q3w (Surgery- rest)	Pembro q3w during chemoRT	Pembro q3w post-chemo-RT	30 days after last dose ³	Obs q3m for 1 yr
			±7	+3	+3	±3	±10	±14
History, physical exam, vital signs, weight, ECOG PS	X	X	X	X	X	X	X	X
Height	X							
Adverse event assessment	X	X	X	X	X	X	X	X
Pregnancy test ⁴	X							
CBC with differential	X	X	X	X	X	X	X	X
Chemistry group ⁵	X	X	X	X	X	X	X	X
Liver function tests ⁶	X	X	X	X	X	X	X	X
Coagulation (PT, aPTT) ⁷	X	X					X	
Thyroid function cascade ⁸	X					X	X	X
Thyroglobulin by mass spec, thyroglobulin antibodies ⁹	X					X	X	X
Urinalysis ¹⁰	X					X	X	
Foundation Medicine (or similar) genomic analyses ¹¹	X							
2D-Echocardiography ¹²	X							
Tumor imaging and measurement ¹³	X					X ¹⁴		X
MRI Brain or CT brain	X							
Research blood specimens (see Section 14.0) ^R			X		X ¹⁵	X ¹⁶	X	

¹ Cycle = 21 days; All tests and procedures are clinically indicated, unless noted with an R to indicate funding by research.

² Laboratory tests (except research blood specimen collection) conducted by sites outside of Mayo Clinic are acceptable if conducted within 7 days of the start of Cycle 1

³ All patients will be followed for aftereffects of immunotherapy for the duration of their care.

⁴ For persons of childbearing potential only; must be done ≤7 days prior to registration.

⁵ Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium

⁶ AST, alkaline phosphatase, total and direct bilirubin

⁷ Coagulation is required at baseline, then as clinically indicated

⁸ Thyroid function testing every 6 weeks to monitor effects of pembrolizumab or as clinically indicated.

⁹ Thyroglobulin testing can be done every 6 weeks or as clinically indicated.

¹⁰ Urinalysis for protein, glucose, blood every 6 weeks or as clinically indicated

¹¹ Optional, can be conducted at any time while on study

¹² Only if results are not available for a 2D Echocardiography test conducted within 3 months prior to registration

¹³ PET/CT or MRI neck or CT neck + CT chest and abdomen and pelvis; initial tumor imaging ≤14 days prior to registration; Use same imaging technique throughout the study

¹⁴ Imaging is to be performed before first dose of pembrolizumab and after chemoRT is done; then q9wks or as clinically indicated during treatment, and q3mo during observation.

Tests and procedures ¹	Active Monitoring Phase						Obs q3m for 1 yr
	≤14 days prior to registration	Pembro (Cycle 1) ²	Pembro q3w (Surgery- rest)	Pembro q3w during chemoRT	Pembro q3w post-chemo-RT	30 days after last dose ³	
Research tissue specimens (see Section 17.0) ^R	X		X		X ¹⁷	X ¹⁸	

4.2 ATC Test Schedule - Cohort B without Surgery

Tests and procedures ¹⁹	Active Monitoring Phase					
	≤14 days prior to registration	Pembro (Cycle 1) ²⁰	Pembro q3w during chemoRT	Pembro q3w post-chemo-RT	30 days after last dose	Obs q3m 1 yr
Window		±7	±3	±3	±10	±14
History, physical exam, vital signs, weight, ECOG PS	X	X	X	X	X	X
Height	X					
Adverse event assessment	X	X	X	X	X	X
Pregnancy test ²¹	X					
CBC with differential	X	X	X	X	X	X
Chemistry group ²²	X	X	X	X	X	X
Liver function tests ²³	X	X	X	X	X	X
Coagulation (PT, aPTT)	X	X			X	
Thyroid function cascade ²⁴	X			X	X	X
Thyroglobulin by mass spec, thyroglobulin antibodies ²⁵	X			X	X	X
Urinalysis ²⁶	X			X	X	

¹⁵ One time prior to Cycle 3 Day 1 of pembrolizumab

¹⁶ One time prior to first post-chemoRT dose of pembrolizumab

¹⁷ Optional, only on first pembro cycle post-chemo-RT if clinical biopsy performed

¹⁸ Optional, if clinical biopsy performed

¹⁹ **Cycle = 21 days;** All tests and procedures are as clinically indicated, unless noted with an R to indicate funding by research

²⁰ Laboratory tests conducted by sites outside of Mayo Clinic are acceptable if conducted within 7 days of the start of Cycle 1

²¹ For persons of childbearing potential only; must be done ≤7 days prior to registration

²² Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium

²³ AST, alkaline phosphatase, total and direct bilirubin

²⁴ Thyroid function testing every 6 weeks to monitor effects of pembrolizumab or as clinically indicated.

²⁵ Thyroglobulin testing can be done every 6 weeks or as clinically indicated.

Tests and procedures ¹⁹	Active Monitoring Phase					
	≤14 days prior to registration	Pembro (Cycle 1) ²⁰	Pembro q3w during chemoRT	Pembro q3w post-chemo-RT	30 days after last dose	Obs q3m 1 yr
Foundation Medicine (or similar) analyses ²⁷	X					
2D-Echocardiography ²⁸	X					
Tumor imaging and measurement ²⁹	X			X ³⁰		X
MRI Brain or CT brain	X					
Research blood specimens (see Section 14.0) ^{31,R}		X	X ³²	X ³³	X	
Research tissue specimens (see Section 17.0) ^{34,R}	X			X ³⁵	X ³⁶	

4.3 Event Monitoring/Survival Follow-up

	Event Monitoring Phase ¹				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

5.0 Grouping Factor

Cohort: A (with surgery) vs. B (no surgery)

²⁶ Urinalysis for protein, glucose, blood every 6 weeks or as clinically indicated

²⁷ Optional, can be conducted at any time while on study

²⁸ Only if results are not available for a 2D Echocardiography test conducted within 3 months prior to registration

²⁹ PET/CT (or MRI neck or CT neck and CT chest + abdomen and pelvis); Initial tumor imaging ≤14 days prior to registration; Use same imaging technique throughout the study

³⁰ Imaging is to be performed before first dose of pembrolizumab after chemoradiation and then every 9 weeks or as clinically indicated during protocol treatment, and every 3 months during observation period.

³¹ Blood specimens will be collected and submitted per Section 14.0

³² One time prior to Cycle 3 Day 1 of pembrolizumab

³³ Only on first post chemoRT cycle

³⁴ Tissue specimens must be collected and submitted per Section 17.0

³⁵ Optional, only on first post-chemoRT cycle if clinical biopsy performed

³⁶ Optional if clinical biopsy performed

6.0 Registration/Randomization Procedures

6.1 Registration

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office a [REDACTED] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [REDACTED] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [REDACTED]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval of the study
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office ([REDACTED]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Correlative studies

- 6.41 A mandatory translational research component is part of this study; the patient will be automatically registered onto this component (Sections 3.19d, 14.0, 17.0).
- 6.42 An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.0) :

Patient has/has not given permission to give his/her tissue sample for research testing.

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of cancer at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.5 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist or radiation oncologist

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.0) must be documented and graded.

6.9a Study drug is available on site

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Treatment medication table

Agent	Dose Level	Route	ReRx
Pembrolizumab	200 mg	IV	q3w

Cycle = 21 days

Note: All cycles will be based on pembrolizumab given once every three weeks. Chemo and radiation therapy may be given as clinically indicated and any delays are per physicians' discretion. Such delays do not affect the cycle length of pembrolizumab.

7.12 Cycle 1 - Prior to surgery (Cohort A) or chemoradiation (Cohort B)

Agent	Dose Level	Route	ReRx
Pembrolizumab	200 mg	IV	q3w

All enrolled patients will undergo treatment with one dose of pembrolizumab 200 mg IV once as soon as possible, at least ≥ 3 days prior to undergoing surgical resection or starting radiation therapy.

NOTE: Patients will sometimes require emergency debulking surgery for impending airway obstruction or any threatening disease to vital structures in neck including vasculature and can undergo surgery emergently within those 3 days. If no surgery is planned or indicated, subjects should proceed with chemoradiation, see Section 7.14 below.

7.13 Surgery for Cohort A – per clinical indications

Agent	Dose Level	Route	ReRx
Pembrolizumab	200 mg	IV	q3w

Surgery should occur approximately 3 days after pembrolizumab dose given in Cycle 1. Surgical recovery period is expected to be approximately 42 days or less.

Pembrolizumab dosing should continue every 3 weeks throughout this period.

7.14 During chemoradiation– per clinical indications

Agent	Dose Level	Route	ReRx
Pembrolizumab	200 mg	IV	q3w

AND

Suggested Chemotherapy Agents	Dose Level	Route	ReRx
Docetaxel	20 mg/m ²	IV	q1w
Doxorubicin	20 mg/m ²	IV	q1w

OR

Suggested Chemotherapy Agents	Dose Level	Route	ReRx
Docetaxel	60 mg/m ²	IV	q3w
Doxorubicin	60 mg/ m ²	IV	q3w

Pembrolizumab 200 mg IV every 3 weeks will be continued throughout chemoradiation therapy. Pembrolizumab can be given concurrently on the days of chemotherapy.

All patients will undergo the standard chemoradiation therapy administered at Mayo Clinic which includes radiation therapy concurrently administered with combination chemotherapy (doxorubicin plus docetaxel, 20 mg/m² each, weekly, or 60 mg/m² every 3 weeks with growth factor support at the discretion of treating provider).

Chemotherapy will stop once chemoradiation is completed. Only pembrolizumab will continue in post-chemoradiation phase as per Section 7.16 below.

7.15 Radiation Therapy – per clinical indications

Radiation therapy will be administered daily, 5 days a week for 6.5 weeks, 33 treatments, total dose 66 Gy to gross disease or high risk postoperative regions (2 Gy per treatment) and 59.4 Gy to areas potentially harboring subclinical disease (1.8 Gy per treatment). If there is no gross disease (postoperative adjuvant setting), the dose will be 60 Gy in 30 treatments to the operative volume (2 Gy per treatment) and 54 Gy in 30 treatments to areas potentially harboring subclinical disease (1.8 Gy per treatment). As indicated, the first few treatments may be administered using highly conformal 3D radiation therapy while waiting for insurance approval for IMRT, or while waiting for an IMRT plan. In cases where IMRT coverage is denied by the insurer, highly conformal 3D radiation therapy techniques may be utilized for the entire treatment. BID treatments (≥6 hours between treatments) or weekend treatments are allowed to compensate for treatment breaks.

7.16 Post-chemoradiation

Agent	Dose Level	Route	ReRx
Pembrolizumab	200 mg	IV	q3w

Following the multimodality therapy pembrolizumab at 200 mg IV every 3 weeks will continue to be administered per disease status given below:

7.161 If no residual disease is found, pembrolizumab will be administered for a total of 17 doses or progressive disease or unacceptable adverse events, whichever is first

7.162 If there is residual disease, pembrolizumab will be administered for a maximum of 35 doses or until progressive disease or unacceptable adverse events; whichever is first.

NOTE: Residual disease is defined in [Section 11.33](#).

7.2 Description of chemoradiation – per Mayo Clinic clinical care standards for ATC

7.21 Chemotherapy with doxorubicin and docetaxel

Intravenous chemotherapy with 20 mg/m² of doxorubicin and docetaxel each will be administered every week during chemoradiation therapy along with pembrolizumab as mentioned in Section 7.14 above. Both chemotherapy and radiation will commence as soon as the possible with regards to tissue healing and per surgeon's recommendations.

Alternatively, chemotherapy also could be administered every three week at 60 mg/m² of doxorubicin and docetaxel each (with growth factor support). This may be sometimes be required to achieve rapid response, and is at the discretion of treating provider.

7.22 Radiation therapy with IMRT

Radiation therapy will be administered daily, 5 days a week for 6.5 weeks, 33 treatments, total dose 66 Gy to gross disease or high risk postoperative regions (2 Gy per treatment) and 59.4 Gy to areas potentially harboring subclinical disease (1.8 Gy per treatment). If there is no gross disease (postoperative adjuvant setting), the dose will be 60 Gy in 30 treatments to the operative volume (2 Gy per treatment) and 54 Gy in 30 treatments to areas potentially harboring subclinical disease (1.8 Gy per treatment). As indicated, the first few treatments may be administered using highly conformal 3D radiation therapy while waiting for insurance approval for IMRT, or while waiting for an IMRT plan. In cases where IMRT coverage is denied by the insurer, highly conformal 3D radiation therapy techniques may be utilized for the entire treatment. BID treatments (≥ 6 hours between treatments) or weekend treatments are allowed to compensate for treatment breaks. Radiation therapy must begin with combination chemotherapy per standard clinical practice. If radiation therapy is delayed, chemotherapy can begin up to 7 days prior to radiation therapy. Radiation Dose and planning suggestions for IMRT are in [Appendix III](#).

7.23 RT Quality Assurance Reviews

The study co-chair, [REDACTED] will perform RT Quality Assurance Reviews per clinical standard of care.

7.3 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation during treatment per the study calendar in [Section 4.0](#) and every 3 months during observation (Active Monitoring Phase).

7.4 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in the following tables until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

→ ***ALERT:*** *ADR reporting may be required for some adverse events (See Section 10.0)* ←

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 4.0* unless otherwise specified* ← ←

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications.etc.htm

8.1 Dose modification for Radiation Therapy

Radiation should be continued unless the patient has serious life threatening complications. Please contact study co-chair [REDACTED] if questions.

8.2 Dosage modifications for pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per the Table below. See [Section 9.0](#) for supportive care guidelines, including use of corticosteroids.

Table 8.21 Dose Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Gastrointestinal disorders	Diarrhea or Colitis	2-3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
Investigations	AST, or ALT, or Blood bilirubin	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose.
		3-4	Permanently discontinue (see exception below) ^a	Permanently discontinue pembrolizumab
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable.

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	2-4	AE resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Endocrine disorders	Hyperthyroidism	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Hypothyroidism	2	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
General disorders and administration site conditions	Infusion related reaction	2 ^b	AE resolves to Grade 0-1	Permanently discontinue if AE develops despite adequate premedication
		3-4	Permanently discontinue	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	1	AE resolves to Grade 0	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		2-4	Permanently discontinue	Permanently discontinue
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e.g. Renal failure or Nephritis)	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue	Permanently discontinue
	All Other Drug-Related Adverse Events ^c	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

^a For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients

should be discontinued.

^b If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.

^c Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

8.21 Other instructions for pembrolizumab

If pembrolizumab-related toxicity does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy discontinuation is recommended. With Investigator agreement, patients with a laboratory adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled.

For patients who experience a recurrence of the same severe AEs listed above with rechallenge of pembrolizumab, a consultation with the Investigator will occur to determine whether the patient should continue in the study. A patient who experiences the same SAE of the same NCI CTCAE grade or higher with rechallenge of pembrolizumab must discontinue pembrolizumab immediately. Reduced dose of pembrolizumab dose (ie, below 200 mg) will not be administered.

8.3 Dose modifications for doxorubicin and docetaxel

8.31 Suggested dose levels for chemotherapy*

Dose Level	Doxorubicin	Docetaxel
Starting Dose	20 mg/m ² weekly or 60 mg/m ² every 3 weeks (with growth factor support)	20 mg/m ² weekly or 60 mg/m ² every 3 weeks (with growth factor support)
-1	-25%	-25%
-2	-50%	-50%

*These levels are guidelines only

8.32 Chemotherapy table of events and modifications for Doxorubicin and Docetaxel

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT ^a	ACTION
Blood and lymphatic disorders	Febrile neutropenia (fever without clinically or microbiologically documented infection) [ANC <1.0 X 10 ⁹ C/L] fever ≥38.3°C)	Doxorubicin and/or Docetaxel	Delay chemotherapy by 1 week until ANC recovers to Grade 0-2 and until fever resolves. Reduce dose by 25% or more for subsequent cycles.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT ^a	ACTION
Cardiac Disorders	Left ventricular systolic dysfunction	Doxorubicin and/or Docetaxel	Grade 3 discontinue doxorubicin, and continue docetaxell with careful monitoring; grade 4 discontinue chemotherapy.
	Atrioventricular block first degree	Doxorubicin	Grade ≥ 3 Discontinue doxorubicin, continue Docetaxel
Gastrointestinal disorders	Vomiting \geq Grade 3	Doxorubicin and/or Docetaxel	If not controlled with optimal medication Reduce dose by 25% and use reduced level for subsequent cycles
Immune system disorders	Allergic reaction Grade 1 (eg, mild flushing, rash, pruritis)	Doxorubicin and/or Docetaxel	Stop infusion After recovery restart the infusion at a rate of 20 ml/h for 15 minutes then 50 ml/h for 15 minutes then, if no further symptoms, at full dose rate until infusion is complete
	Allergic reaction Grade 2-3 (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	Doxorubicin and/or Docetaxel	Stop infusion Give IV antihistamine (diphenhydramine 50 mg IV), IV H2-receptor antagonist (famotidine 20 mg IV) and steroid (dexamethasone 10 mg IV) After recovery of symptoms resume docetaxel infusion at a rate of 20 ml/h for 15 minutes then 50 ml/h for 15 minutes then, if no further symptoms, at full dose rate until infusion is complete
	Anaphylaxis (e.g. one or more of the following): respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	Doxorubicin and/or Docetaxel	Stop infusion give IV antihistamine (diphenhydramine 50 mg IV), IV H2-receptor antagonist (famotidine 20 mg IV) and steroid (dexamethasone 10 mg IV) Add epinephrine or bronchodilators if indicated, report as an adverse event Discontinue doxorubicin and/or docetaxel.
Investigations	Neutrophil count decreased \geq Grade 3 (ANC 500 to $<1000/\text{mm}^3$)	Doxorubicin and/or Docetaxel	Delay chemotherapy by 1 week until recovery to Grade 0-2 Consider reducing dose by 25% for subsequent cycles
	Platelet count decreased \geq Grade 2 ($<75 \times 10^9/\text{L}$)	Doxorubicin and/or Docetaxel	Delay chemotherapy by 1 week until recovery to Grade 1 Consider reducing dose by 25% for subsequent cycles
Investigations	Bleeding \geq Grade 3 or requiring ≥ 2 platelet transfusions	Doxorubicin and/or Docetaxel	Delay chemotherapy by 1 week until bleeding recovers to Grade 0-1 Permanently discontinue chemotherapy, or reduce dose by 25% or more for subsequent cycles

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT ^a	ACTION
Nervous system disorders	Peripheral motor neuropathy Grade 2	Docetaxel	Reduce dose by 25% and use reduced level for subsequent cycles
	Peripheral motor neuropathy Grade 3 or higher	Docetaxel	Discontinue docetaxel
All other non-hematologic ^b	≥Grade 3	Doxorubicin and/or Docetaxel	Discontinue chemotherapy, or reduce dose by 25% or more and use reduced dose for subsequent cycles

^a If a drug is held, omitted, discontinued or dose-reduced, it is the physician's discretion to apply the modification to one or both cytotoxic drugs, and the decision should depend on the nature and severity of the particular adverse event and its likely causal relation to the agent.

^b For adverse effects ≥Grade 3 commonly associated with radiation such as radiation dermatitis, dry mouth, mucositis, thick secretions/saliva, loss of taste, weight loss, loss of appetite dose modifications for chemotherapy will be at the discretion of the treating physician.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 8.2 for dose modification.

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

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947.

9.21 Neutropenia

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

9.22 Anemia

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

9.23 Thrombocytopenia

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

9.3 Anti-infectives

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

9.4 Corticosteroids

Patients may continue on steroid inhalation therapy. Systemic corticosteroids are known immunosuppressive agents that can mitigate the effects of pembrolizumab. Steroids should be generally reserved to treat side effects of pembrolizumab. Steroids can be used as primary prevention of nausea per institutional guidelines, but steroid doses should be reduced in subsequent cycles if nausea/vomiting is absent or very mild (see Section 9.5).

9.5 Antiemetics

Antiemetics may be used at the discretion of the attending physician. Nausea and vomiting should be treated aggressively, and consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Volume depletion should be corrected before initiation of study drug.

If no or minimal nausea/vomiting is reported after first dose of chemotherapy, investigators are strongly encouraged to reduce the dose of dexamethasone to 10 mg as pre-treatment anti-emetic dosing on Day 8. In addition, if nausea/vomiting continues to be a minimal issue, investigators are strongly encouraged to progressively decrease the pre-treatment dose of dexamethasone in subsequent doses (eg, 8 mg, 6 mg, 4 mg, 2 mg, or zero).

9.6 Anti-diarrheals

Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. (See Section 9.7 for management of treatment-related enterocolitis)

All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

NOTE: Loperamide/diphenoxylate/atropines should NOT be used for diarrhea symptoms unless: (1) it is believed that pembrolizumab-related enterocolitis is unlikely to be present after detailed evaluation by gastroenterology, including endoscopy; PLUS (2) approval is documented by a gastroenterology specialist.

9.7 Immunotherapy-related toxicities

Patients should be monitored for signs and symptoms of immunotherapy-related toxicities, which include but are not limited to the following:

- **Pneumonitis**
 - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
 - For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
 - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/colitis**

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

 - All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
 - For Grade 2 diarrhea/colitis, administer oral corticosteroids.
 - For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
 - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

For T1DM or **Grade 3-4** Hyperglycemia:

 - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
 - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**
 - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
 - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or hypothyroidism**

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

 - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
 - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4 hyperthyroidism**
 - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**
 - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
 - Treat with IV or oral corticosteroids
 - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
 - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal failure or nephritis**
 - For **Grade 2** events, treat with corticosteroids.
 - For **Grade 3-4** events, treat with systemic corticosteroids.
 - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.8 Management of treatment related enterocolitis

In patients with severe enterocolitis, pembrolizumab will be held and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In patients with moderate enterocolitis, pembrolizumab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

9.9a Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

9.9a1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10.

9.9a2 Prohibited Concomitant Medications

The following medications are **not** permitted during the screening and treatment phase (including retreatment for post-complete response relapse) of this trial:

- Anti-neoplastic systemic cytotoxic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the principal investigator.

NOTE: Use of steroids during chemoradiation for controlling chemotherapy-associated nausea and docetaxel associated edema is allowed.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

9.9b Infusion Reaction

Table 9.9b Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of	Subject may be premedicated 1.5h (\pm 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	<p>stopping treatment infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.</p> <p>Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</p>	
<p><u>Grades 3 or 4</u></p> <p>Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</p> <p>Grade 4: Life-threatening; pressor or ventilatory support indicated</p>	<p>Stop Infusion Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p> <p>Hospitalization may be indicated.</p> <p>Subject is permanently discontinued from further trial treatment administration.</p>	No subsequent dosing

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study treatment administration.

9.9c Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

Female patients will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the

absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

9.9d Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Mayo Clinic and to Merck without delay and within 24 hours to Mayo Clinic and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Mayo Clinic and to Merck and followed as described above.

9.9e Use in Nursing Adults

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

9.9e1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

9.9e2 Docetaxel and Doxorubicin

Doxorubicin has been reported to be found in human milk; patients receiving doxorubicin injection should not breast-feed. It is unknown if docetaxel is excreted in human milk, it is recommended that breast feeding be discontinued.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 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)

- a. Identify the grade and severity of the event using the CTCAE version 4.0.
- b. Determine whether the event is expected or unexpected (see Section 10.2).
- c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
- d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
- e. Determine if other reporting is required (see Section 10.5).
- f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

- Definite - The AE *is clearly related* to the agent(s)/procedure.
- Probable - The AE *is likely related* to the agent(s)/procedure.
- Possible - The AE *may be related* to the agent(s)/procedure.
- Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
- Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting-**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>

or

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm>

Instructions for completing the MedWatch 3500A:

<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf>

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported ¹
General disorders and administrations site conditions	Fatigue	Grade 3
Gastrointestinal	Vomiting	Grade 3
	Nausea	Grade 3
	Oral mucositis	Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	Weight loss	Grade 3
Injury, poisoning, and procedural complications	Radiation dermatitis	Grade 3
Blood and lymphatic system disorders	Anemia	≤Grade 4

¹ These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed. Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no “adverse event” (*i.e.*, there is no onward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

<p>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 				
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	7 Calendar Days		
<p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> o "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. o "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE. 				
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-hour notification followed by complete report within 3 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 7 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events <p>² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.</p>				
<p>Effective Date: May 5, 2011</p>				

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Submit form MedWatch 3500A to the FDA, [REDACTED] or online at

<http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>.

Use Mayo Expedited Event Report form

<http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56> for investigational agents or commercial/investigational agents on the same arm and attach MedWatch 3500A.

Submit to Merck Global Safety (Attn: Worldwide Product Safety Fax [REDACTED])

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously

reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO complete Mayo Clinic Cancer Center SAE Reporting Form

and attach appropriate documentation for [REDACTED] The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified-

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as “A disorder characterized by cessation of life occurring during the first 28 days of life” that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 “General disorders and administration - Other (neonatal loss)”** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.

Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

CTCAE SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Febrile neutropenia		X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
	Mucositis oral		X
General disorders and administration site conditions	Fatigue	X	X
Infections and infestations	Sepsis		X
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Nervous system Disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X
Skin and subcutaneous tissue disorders	Rash, maculo-papular	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

- 10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- 10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Merck Additional Event Reporting Instructions

10.81 Events of Clinical Interest (ECIs)

ECIs are selected non-serious and serious adverse experiences that must be reported within 24 hours to Mayo Clinic via email and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety [REDACTED]).

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 10.82, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

10.82 Reporting of Overdose of Pembrolizumab

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥ 5 times the indicated dose). No specific

information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to Mayo Clinic [REDACTED] and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; [REDACTED])

10.83 Additional Instructions for AE Reporting to Merck

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event
- Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified

safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the **Merck Global Safety facsimile number:** [REDACTED]

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

11.0 Treatment Evaluation Using RECIST Guidelines

NOTE: This study uses RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measurable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)(Eisenhauer, Therasse et al. 2009) . Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

NOTE: The primary mass and irradiated lymph nodes in neck and upper mediastinum will be non-measurable.

11.1 Schedule of Evaluations

Screening (before surgery or chemoradiation): Baseline scan to assess the disease status should have been performed within 14 days prior to registration. An FDG PET-CT, or CT scan of neck, chest and abdomen and pelvis should be obtained. MRI of the neck is acceptable in lieu of CT-neck but not preferred.

Post-chemoradiation: The first scan after treatment initiation will be performed at the completion of chemoradiation. During protocol treatment scans should be performed every 9 weeks and then every 3 months in the observation period. Additional scans could be obtained at the discretion of the physician.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 2.0 cm with chest x-ray, or as ≥ 1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is > 1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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 patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis

<1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- 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. The lesions should be measured on the same pulse sequence. 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.
- PET-CT: 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.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' 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:
 - i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
 - ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that

site. In this situation, the date of PD will be the date of the initial abnormal FDG-PET scan.

- iii 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, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- **Residual disease after chemoradiation is defined as persistent primary tumor mass (FDG-avid or nonavid) or any known distant metastatic disease as in AJCC stage IVC.**
- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).
- 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.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in ATC after chemoradiation can represent fibrotic tissue)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.
Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/ must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response.

11.432 Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

- a. Disappearance of all target lesions.
- b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

Progression (PD): At least one of the following must be true:

- a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
- b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

- c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
- a. Disappearance of all non-target lesions.
 - b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- Progression (PD): At least one of the following must be true:
- a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
 - b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
 - c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

11.441 For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.442 For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*See Section 11.431

11.45 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to

document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Treatment Evaluation after Completion of Surgery and Post-operative Chemoradiation (Cohort A patients)

11.51 Definition of Recurrence

The term “recurrence” is used if cancer returns either in the locoregional area of the primary tumor or at distant sites following R0 or R1 resection

11.52 How Recurrence is Determined

Recurrence is determined radiographically and biopsy could be performed at the discretion of treating physician except as detailed below or when CT findings are equivocal in the determination of the enrolling physician.

Locoregional recurrence: Identified by a new soft-tissue mass in the operated thyroid bed or regional cervical lymph nodes. In some cases post-radiation changes may make it difficult to distinguish from early tumor progression. In cases in which the diagnosis is ambiguous, discussion with the PI should occur. Performance of tissue biopsy should be considered prior to assigning a diagnosis of locoregional recurrent disease.

12.0 Descriptive Factors

- 12.1 Associated lymphocytic/autoimmune thyroiditis: Yes vs. no
- 12.2 Coexistent differentiated thyroid cancer: Yes vs. no
- 12.3 Primary tumor resected: Yes vs. no
- 12.4 Prior TKI use: Yes vs. no
- 12.5 Prior/remote/unrelated neck radiotherapy (therapeutic, not diagnostic): Yes vs. no
- 12.6 Prior history of differentiated thyroid cancer: Yes vs. no

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who have not had disease progression and have experienced acceptable toxicity are to continue treatment per protocol until confirmed PD, unacceptable toxicity or refusal. Patients with PD will proceed to EM and others will proceed to observation until PD.

13.2 Progressive disease (PD)

If radiologic imaging verifies initial disease progression per RECIST 1.1 or recurrence after surgery, treatment may continue at the discretion of the Investigator until repeat imaging ≥ 6 weeks later. The Investigator’s decision to continue treatment while awaiting repeat imaging should be based on the subject’s overall clinical condition guided by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No significant decline in ECOG performance status
- Absence of rapid progression of disease

- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If repeat imaging confirms disease progression due to any of the scenarios listed below, patients will be discontinued from study therapy.

- Non-target disease resulting in initial disease progression is worse (qualitative)
- New lesion resulting in initial disease progression is worse (qualitative)
- Additional new lesion(s) since last evaluation

In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions. When feasible, study treatment should not be discontinued until progression is confirmed.

If the initial documented progression is confirmed, patients will go to the event-monitoring phase until death or a maximum of 5 years post-registration.

13.3 Off protocol treatment for reasons other than PD

Patients who go off protocol treatment for reasons other than PD will go to the observation phase for 1 year and then to EM.

13.4 Observation

If the patient has achieved CR, PR, or SD, the patient will continue treatment per protocol and then observed every 3 months for 1 year.

13.5 Duration of therapy for CR

Patients who achieve a CR will complete therapy per protocol. After that, they should be observed (see 13.4 above) every 3 months for 1 year and proceed to event monitoring. If they develop PD during observation, then they will proceed to event monitoring.

13.6 Duration of therapy for PR or SD

Patients who are in PR or SD will continue on therapy per protocol. Subsequent treatment is at the discretion of their attending physician

13.7 CNS PD

Patients who develop PD in the CNS may receive whole brain radiotherapy (WBRT) or gamma-knife radiotherapy and will be considered to have PD and proceed to EM.

13.8 Non-CNS PD

Patients who develop non-CNS PD at any time should go to event monitoring. These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.9b Definition of Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.9c Definition of Major Violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9d Definition of Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Screening (baseline)	Prior to Cycle 3 Day 1 of Pembro	After chemo-RT Prior to next dose of pembro	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immune phenotyping the peripheral blood (Ryder-Dietz lab) ¹	Mandatory	Whole blood	EDTA (lavender)	1 tube, 6 ml	X		X	No	Ambient (do not freeze)
Cytokine alterations in circulation (Ryder-Dietz lab) ¹	Mandatory	Whole blood	Red/gray speckled top (clot activator)	1 tube, 10 ml	X		X	No	Ambient (do not freeze)
Thyroid autoantibody screen (Ryder-Dietz lab) ¹	Mandatory	Whole blood	Red/gray speckled top (clot activator)	1 tube, 10 ml	X		X	No	Ambient
Circulating Tumor cells (Minetta Liu lab) ²	Mandatory	Whole blood	AccuCyte tube	1 tube, 10 ml	X	X	X	No	Ambient

1. MCR only will participate; samples must be delivered to [REDACTED]. Can be collected M-F add [REDACTED].
2. MCR only will participate; samples should be delivered directly to [REDACTED]; personnel [REDACTED], for immediate pick-up ([REDACTED]). Can be collected M-F.

- 14.2 Collection, Processing and Shipping
- 14.21 No kits are required for this study. (Mayo Clinic in Rochester will use Special Study cards in place of kits)
- 14.22 MCR samples can be collected Monday-Friday.
- 14.23 Label specimen tube(s) with protocol number, patient study ID number, and time and date blood is drawn.
- 14.24 Collect and process all blood/blood products according to the protocol.
- 14.25 Shipping (MCA/MCF only) - NA
- 14.3 Other body fluids handling - None
- 14.4 Background and Methodology

Blood/blood product samples will be collected for the following research:

- 14.41 Blood for correlative research (██████████). One 6 ml EDTA tube whole blood and one red 10 ml serum tube specimen should be collected per table 14.1 for analysis of circulating MDSCs and other circulating immune markers. These samples will be collected at baseline and after chemoradiation per table 14.1. This specimen will only be collected at Mayo Rochester; other site(s) will not participate in this portion of the translational study. Whole blood should be sent to the Dietz Lab, where processing will be completed.
- 14.43 Blood for correlative research (██████████). One 10 mL whole blood sample will be collected in AccuCyte Blood Collection Tubes, which contain the proprietary RareCyte cell preservative. These will be collected at baseline, during and after chemoradiation per table 14.1. These samples will be shipped or delivered immediately at ambient temperature to Mayo Clinic Rochester and then processed through the RareCyte system within three days of collection. CTCs will be captured onto glass slides (8 slides per blood sample) for subsequent immunofluorescent staining, selection, and single cell isolation.

Specimens will be collected at the following time points:

- Baseline
- Prior to starting third cycle of pembrolizumab (Cycle 3, Day 1 \pm 3 days)
- Following completion of chemoradiation therapy preferably before next dose of pembrolizumab

15.0 Drug Information

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 Background

Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 Formulation

Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.13 Preparation and storage

Vials should be stored in the refrigerator at temperatures between 2-8°C. Drug concentrate is further diluted with normal saline (or 5% dextrose in the concentration range of 1 to 10 mg/mL) in IV containers made of polyvinyl chloride (PVC) or non-PVC material. The infusion solution in the IV bag should be immediately administered. Pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of reconstituted solution in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

In addition, IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use.

15.14 Administration

Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCl following the completion of the infusion.

15.15 Pharmacokinetic information

a) Absorption – Steady state is predicted to be achieved after ~18 weeks of repeated dosing, with ~2.2-fold accumulation in exposure during administration Q3W relative to exposure observed following single dose administration. The majority (~81%) of this accumulation has occurred by the fourth dose. In the dose range studied for efficacy (2 to 10 mg/kg), pembrolizumab exposure increases in a dose-proportional manner, with clearance being independent of time or pembrolizumab concentration.

b) Distribution – Pembrolizumab has a limited volume of distribution.

c) Excretion – The systemic clearance of pembrolizumab is ~0.22 L/day and the terminal elimination half-life ($t_{1/2}$) is estimated to be ~26 days.

d) Metabolism – Pembrolizumab is catabolized by the general protein degradation processes; typical small molecule metabolic pathways (e.g., cytochrome P450 enzymes, glucuronosyltransferases) do not contribute to its clearance.

15.16 Potential Drug Interactions

There are no known significant drug interactions.

15.17 Known potential toxicities**Common known potential toxicities, >10%:**

Dermatologic: Pruritus, skin rash

Gastrointestinal: diarrhea

Neuromuscular & skeletal: Arthralgia, back pain

Respiratory: Cough

Less common known potential toxicities, 1% - 10%:

Infusion related reactions

Dermatologic: vitiligo, severe skin reactions

Endocrine & metabolic: Hypothyroidism, hyperthyroidism, hyponatremia

Gastrointestinal: Colitis, abdominal pain

Respiratory: Pneumonitis

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Secondary adrenocortical insufficiency (immune-mediated), hepatitis (including autoimmune hepatitis), hypophysitis, nephritis, Guillain-Barre syndrome (immune-mediated), myositis (immune-mediated), pancreatitis (immune-mediated), uveitis (immune-mediated), and Type I diabetes mellitus.

Two important potential risks have been identified, although the data available thus far for these events does not provide sufficient evidence of a causal relationship to pembrolizumab. The two important potential risks are: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and venoocclusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors. The Sponsor continues to monitor and collect data on these potential risks in order to further characterize their potential relationship to pembrolizumab.

Two important updates from additional information from the clinical trial and post-marketing environments include: a) A new important risk of myocarditis. Cases with fatal outcome have been reported. b) Further characterization of the existing important identified risk of severe skin reactions to include cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome.

15.18 Drug procurement

Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 Nursing Guidelines

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen however, is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of

- stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- 15.193 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per [Section 9.0](#) and monitor for effectiveness.
- 15.194 Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- 15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- 15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and “not feeling well.” Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- 15.197 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
- 15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient’s fatigue level prior to each cycle of therapy and report any changes to the study team.
- 15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.
- 15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab
- 15.199c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.2 Doxorubicin

15.21 Background:

Doxorubicin inhibits DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II and by steric obstruction. Doxorubicin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a powerful iron chelator; the iron-doxorubicin complex can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes.

15.22 Formulation:

Commercially available for injection as:
Injection, powder for reconstitution: 10 mg, 50 mg
Injection, solution: 2 mg/mL (5 mL, 10 mL, 25 mL, 100 mL)

15.23 Preparation, storage, and stability:

Refer to package insert for complete preparation and dispensing instructions. Store intact vials of solution under refrigeration and protect from light; store intact vials of lyophilized powder at room temperature. Reconstitute lyophilized powder with NS to a final concentration of 2 mg/mL. Reconstituted vials are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Infusions are stable for 48 hours at room temperature when protected from light. Solutions diluted in 50-1000 mL D5W or NS are stable for 48 hours at room temperature when protected from light. Stable with vincristine in NS for five days at room temperature protected from light.

15.24 Administration

Refer to the treatment section for specific administration instructions. Doxorubicin is administered I.V. push over at least 3-5 minutes, IVPB over 15-60 minutes, or continuous infusion. Avoid extravasation. Flush with 5-10 mL of I.V. solution before and after drug administration. Incompatible with heparin.

15.25 Pharmacokinetic information:

Distribution: V_d : 809-1214 L/m²; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta
Protein binding, plasma: 70% to 76%
Metabolism: Primarily hepatic to doxorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides
Half-life elimination:
Distribution: 5-10 minutes
Elimination: Doxorubicin: 1-3 hours; Metabolites: 3-3.5 hours
Terminal: 17-48 hours
Male: 54 hours; Female: 35 hours
Excretion: Feces (~40% to 50% as unchanged drug); urine (~5% to 12% as unchanged drug and metabolites)
Clearance: Male: 113 L/hour; Female: 44 L/hour

15.26 Potential Drug Interactions:

Cytochrome P450 Effect: Substrate of CYP2D6 (major), 3A4 (major); **Inhibits** CYP2B6 (moderate), 2D6 (weak), 3A4 (weak)

Increased Effect/Toxicity: Bevacizumab, trastuzumab, and cyclophosphamide may enhance the cardiotoxic effect of doxorubicin. Docetaxel and paclitaxel may enhance the adverse/toxic effect of doxorubicin; may increase the serum concentration of doxorubicin and may also increase the formation of toxic doxorubicin metabolites in heart tissue. Cyclosporine and sorafenib may increase the levels/effects of doxorubicin. CYP2D6 inhibitors may increase the levels/effects of doxorubicin. CYP3A4 inhibitors may increase the levels/effects of doxorubicin. Doxorubicin may increase the levels/effects of CYP2B6 substrates.

Decreased Effect: Digoxin may diminish the cardiotoxic effect of doxorubicin. Doxorubicin may decrease the absorption and serum concentration of cardiac glycosides. CYP3A4 inducers may decrease the levels/effects of doxorubicin.

Herb/Nutraceutical Interactions: Avoid St. John's wort (may decrease doxorubicin levels). Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.27 Known potential adverse events

Consult the package insert for the most current and complete information.

Common known potential toxicities, >10%:

Dermatologic: Alopecia

Gastrointestinal: Mucositis, nausea, vomiting

Genitourinary: Discoloration of urine

Hematologic: Leukopenia/neutropenia (75%; nadir: 10-14 days; recovery: by Day 21); thrombocytopenia and anemia

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Congestive heart failure

Central nervous system: Malaise

Dermatologic: Itching, rash, discoloration of saliva, sweat, or tears, radiation recall

Endocrine & metabolic: Amenorrhea, dehydration, infertility (may be temporary), hyperuricemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, GI ulceration, colon necrosis

Local: Skin "flare" at injection site, urticaria

Neuromuscular & skeletal: Weakness

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Dermatologic: Photosensitivity, ulceration or severe reaction at the injection site if extravasation occurs.

15.28 Drug procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing Guidelines:

- 15.291 Check CBC and platelet counts. Instruct patient to watch for signs of infection, bleeding, and anemia.
- 15.292 Advise patient that their urine may turn pink in color for approximately 24 hours after administration of the drug.
- 15.293 Adriamycin is a vesicant. Check IV patency before and frequently during administration. If extravasation occurs, refer to institutional guidelines.
- 15.294 Hair loss occurs 2-4 weeks after initial injection and can be complete. Regrowth begins 2-3 months after discontinuation.
- 15.295 Beware of Adria “flare” that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.
- 15.296 Administer antiemetics to minimize nausea and vomiting.
- 15.297 Assess for alterations in mucous membranes. Stomatitis occurs within 7-10 days after injection. It begins with burning sensation and can progress to ulceration, which can last 3 days. Carafate slurry may be useful. Adequate nutritional counseling is important. Topical anesthetics such as viscous Xylocaine can be used symptomatically.
- 15.298 Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.
- 15.299a Adriamycin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated Cyclophosphamide (Cytosan, CTX) induced hemorrhagic cystitis.
- 15.299b Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alerts to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales. Instruct patients to report any of these signs or symptoms to their health care provider.
- 15.299c Document cumulative dose, which should not exceed maximum cumulative dose.
- 15.299d Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

15.3 Docetaxel (Taxotere®, TATER)

15.31 Background

Antineoplastic Agent, Antimicrotubular, Taxane derivative. Docetaxel promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

15.32 Formulation

Note: Docetaxel is now available as a one-vial formulation in two concentrations: 10 mg/mL and 20 mg/mL. The older formulation included 2 vials which consisted of a concentrated docetaxel vial and a diluent vial, resulting in a reconstituted concentration of 10 mg/mL. Admixture errors could occur due to the concentration difference between the new formulations of 10 mg/mL and 20 mg/mL and the old formulation (10 mg/mL). Do not use the two-vial formulation with the one-vial formulation for the same admixture product.

15.33 Preparation, storage, and stability

Storage conditions: Store the packaged docetaxel between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

One-vial formulation: Note: One-vial formulation is available in two concentrations: 10 mg/mL and 20 mg/mL. Further reconstitution with diluent is not required. Further dilute for infusion in 250-500 mL of NS or D₅W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Solutions prepared from the one-vial formulation and diluted for infusion should be used within 4 hours of preparation (infusion should be completed within 4 hours).

15.34 Administration

Administer IV infusion over 1-hour through nonsorbing polyethylene lined (non-DEHP) tubing; in-line filter is not necessary. **Note:** Premedication with dexamethasone 8 – 10 mg orally twice daily for 3-5 days, beginning the day before docetaxel administration is recommended to decrease the incidence and severity of fluid retention and prevent hypersensitivity reactions and pulmonary/peripheral edema. When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy. Infusion should be completed within 4 hours of final preparation.

15.35 Pharmacokinetic information

Docetaxel exhibits linear pharmacokinetics at the recommended dosage range.

Distribution: Extensive extravascular distribution and/or tissue binding; V_d : 80-90 L/m², V_{dss} : 113 L (mean steady state)

Protein binding: ~94% to 97%

Metabolism: Hepatic; oxidation via CYP3A4 to metabolites

Half-life elimination: Terminal: ~11 hours

Excretion: Feces (~75%, <8% as unchanged drug); Urine (~6%)

15.36 Potential Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP3A4; **Inhibits** CYP3A4 (weak).

Increased Effect/Toxicity: CYP3A4 inhibitors may increase the levels/effects of docetaxel. Concomitant use of docetaxel with a potent CYP3A4 inhibitor should be avoided. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, a 50% reduction in docetaxel dose should be considered along with close monitoring for docetaxel toxicity. Refer to the package insert or LexiComp¹ for example inhibitors. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Taxane derivatives may enhance the adverse/toxic effect of anthracyclines.

Decreased Effect: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp¹ for example inducers.

Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (due to GI irritation). Avoid St John's wort (may decrease docetaxel levels).

Immunosuppressants: (ex: denosumab, pimecrolimus, tacrolimus, etc.) docetaxel may enhance the adverse/toxic effect of immunosuppressants (risk for serious infections may increase)

Myelosuppressed Agents: increased risk of agranulocytosis and/or pancytopenia (ex: clozapine, dipyrene)

BCG: Immunosuppressants may diminish the therapeutic effect of BCG

Treatment with Docetaxel Products May Cause Symptoms of Alcohol Intoxication June 2014

The FDA is warning health care providers and patients that docetaxel injection products contain ethanol, which may cause patients to experience symptoms of alcohol intoxication during and after treatment. The FDA is revising the labels of all docetaxel drug products to warn about this risk. Health care providers should consider the alcohol content of docetaxel products when prescribing or administering the drug to patients, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications. Patients should avoid driving, operating machinery, or performing other activities that are dangerous for one to two hours after docetaxel infusion.

15.37 Known potential adverse events

Consult the package insert for the most current and complete information. Percentages reported for docetaxel Monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication. The incidence of adverse events was usually higher in patients with elevated liver function tests.

Common known potential toxicities, >10%:

Cardiovascular: Fluid retention

Central nervous system: Neurosensory events including neuropathy, fever, neuromotor events.

Dermatologic: Alopecia, cutaneous events, nail disorder

Gastrointestinal: Stomatitis, diarrhea, nausea, vomiting

Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia

Hepatic: Transaminases increased

Neuromuscular & skeletal: Weakness, myalgia

Respiratory: Pulmonary events

Miscellaneous: Infection, hypersensitivity

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Left ventricular ejection fraction decreased, hypotension

Central nervous system: Peripheral motor neuropathy

Dermatologic: Rash/erythema

Gastrointestinal: Taste perversion

Hepatic: Bilirubin increased, alkaline phosphatase increased

Local: Infusion-site reactions including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein

Neuromuscular and skeletal: Arthralgia

Ocular: Epiphora associated with canalicular stenosis

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Acute myeloid leukemia, acute respiratory distress syndrome, anaphylactic shock, angina, ascites, atrial fibrillation, atrial flutter, bleeding episodes, bronchospasm, cardiac tamponade, chest pain, chest tightness, colitis, conjunctivitis, constipation, cutaneous lupus erythematosus, deep vein thrombosis, dehydration, disseminated intravascular coagulation, drug fever, duodenal ulcer, Dyspnea, dysrhythmia, ECG abnormalities, erythema multiforme, esophagitis, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hand and foot syndrome, hearing loss, heart failure, hepatitis, hypertension, ileus, intestinal pneumonia, ischemic colitis, lacrimal duct obstruction, loss of consciousness (transient), MI, multiorgan failure, Myelodysplastic syndrome, neutropenic enterocolitis, ototoxicity, pleural effusion, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall, renal insufficiency, seizure, sepsis, sinus tachycardia, Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, tachycardia, thrombophlebitis, unstable angina, visual disturbances (transient)

15.38 Nursing guidelines

- 15.381 Monitor CBC closely, as neutropenia, and thrombocytopenia are common and may be life threatening, and dose limiting. Instruct patient to report any signs or symptoms of infection, any unusual bruising, or bleeding.
- 15.382 Administer antiemetics as ordered. Evaluate for their effectiveness.
- 15.383 Monitor for signs/symptoms of hypersensitivity reactions that may include chills, rigors, dyspnea, bronchospasms, etc. Stop infusion immediately and administer proper emergency treatment.
- 15.384 Because of the risk of anaphylaxis and development of edema, instruct patient that is imperative to take steroid premedications as ordered. Decrease in steroids has been recommended in this protocol. Please follow guidelines as mentioned in [Section 9.5](#).
- 15.385 Instruct patient on proper oral care, as mucositis may occur.
- 15.386 Advise patient about alopecia.
- 15.387 Monitor liver function tests.

- 15.388 Drug is a vesicant. Monitor infusion site frequently for signs of irritation or infiltration. Drug extravasation causes acute streaking, burning pain, and discoloration at the site. Skin may be reddened for several weeks and occasionally blister and/or peel. Reactions are usually reversible over time. Because of this central venous access may be necessary. Discuss with MD if patient has poor peripheral venous access. If docetaxel concentrate or diluted solution comes into contact with skin, wash with soapy water immediately. If it comes into contact with mucosa, wash with warm water immediately.
- 15.389a Instruct patient to report any signs of peripheral neuropathy to the health care team (pain, numbness, tingling).
- 15.389b Monitor for signs and symptoms of fluid retention, weight gain, ascites and CHF.
- 15.389c Instruct patient about possible facial flushing, rash, and skin and nail changes. Monitor for signs and symptoms of hand/foot syndrome. However premedication with steroids can minimize this side effect. Discuss with MD possible ways to manage itching and skin changes that may occur up to a week after docetaxel administration. Advise patients that nails may crack, peel, or fall off all together. This may be a chronic toxicity. Instruct patient to keep nails clean, short and to avoid wearing nail polish or artificial nails.
- 15.189d In case of overdose, patient should be hospitalized and vital signs monitored.

16.0 Statistical Considerations and Methodology

16.1 Statistical Design

A one stage design with an interim analysis based on the Simon's optimal design (Simon 1989) was chosen to demonstrate efficacy of pembrolizumab in improving overall survival in combination with standard chemo-radiotherapy in ATC in comparison to historical cohort. This design will permit early stopping of the trial if there is strong evidence that the study regimen is inactive.

16.11 Primary endpoint

The primary endpoint is the 6-month overall survival rate in Cohort A and B combined. The 6-month overall survival rate is defined as the total number of efficacy evaluable patients who are alive 6 months from registration divided by the total number of efficacy evaluable patients enrolled on study. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for 6-month overall survival.

16.12 Operating Characteristics

ATC has dismal prognosis and has the historical median OS of 6 months (Goutsouliak and Hay 2005; Foote, Molina et al. 2011; Sherman, Lim et al. 2011). It is designed as a one-sided test to detect a $\geq 48.5\%$ reduction of the hazard rate associated with overall survival (OS) when compared to historical median OS of 6 months, favoring the addition of pembrolizumab. To evaluate ATC, the largest 6-months overall survival rate where the addition of pembrolizumab would be considered ineffective in this population is 50%, and the smallest that would warrant further subsequent studies is 70%. The study design proposed below yields an 80% chance of detecting that the 6-month overall survival rate is at least 70% at a one-sided 0.2 significance level.

We will have two cohorts, Cohort A, for patients who will undergo surgery and chemoradiation here at Mayo, and Cohort B, patients in whom surgery is not indicated (mostly because of involvement of critical structures in neck). The following decision rule is applied to patients in Cohort A and B combined:

- 16.121 Interim Analysis: Enter 10 eligible patients. If more than 6 of the first 10 evaluable patients enrolled are alive at 6 months then we would proceed with accrual. If not, patient accrual will be terminated and the regimen would be considered inactive in this patient population
- 16.122 Final Analysis: Enter an additional 10 eligible patients. If at least 12 of the total 20 evaluable patients enrolled are alive at 6 months, consideration would be given to recommending this treatment for further testing in this patient population. If 11 or fewer patients enrolled are alive at 6 months, we will consider this regimen ineffective in this patient population.
- 16.123 Overaccrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.
- 16.124 NOTE: The trial will not be halted while the first 10 patients are evaluated for the interim analysis. However, if the accrual is especially

rapid, we may temporarily suspend accrual to prevent missing important acute toxicity patterns.

16.13 Power and Significance Level

Assuming that the number of 6-month survivor is binomially distributed, the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various tumor response rates and the probability of stopping accrual after the first stage can be tabulated as a function of the true tumor response rates as shown in the following table.

If the true 6-month survival rate is	45%	50%	55%	60%	65%	70%	75%
Then the probability of declaring that the regimen warrants further study is...	0.10	0.20	0.33	0.50	0.66	0.80	0.91
And the probability of stopping at the completion of stage 1 is...	0.74	0.62	0.50	0.37	0.25	0.15	0.08

16.14 Sample Size

A total of 20 evaluable patients will be accrued in Cohort A and B combined per study design, unless the study is permanently closed at interim analysis or undue toxicity is observed. We anticipate accruing an additional 5 patients in order to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 25 patients for this trial.

16.15 Accrual Time and Study Duration

No similar studies have been conducted for comparison. Based on our anecdotal experience from referrals of patients from outside institutions who would otherwise fit eligibility criteria we believe we will be able to enroll 1 patient per month at our institution (Mayo Clinic). We believe we can complete accrual within the proposed 2-year period.

16.2 Analysis Plan

16.21 Primary Endpoint

16.211 Definition: The primary endpoint of this trial is the overall survival rate at 6 months. This is defined as the proportion of evaluable patients who are alive at 6 months. We consider a success to be alive. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be considered evaluable.

16.212 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated.

16.22 Definitions and analyses of secondary clinical endpoint

Safety and tolerability of pembrolizumab with chemoradiotherapy: All adverse events will be graded using the NCI CTCAE Version 4.0. For each type of adverse event classified as either possibly, probably, or definitely related to study treatment, the proportion of patients experiencing a severe (Grade 3 or higher) adverse event will be noted per cycle. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine adverse event patterns.

16.23 Exploratory endpoints:

- 16.231 Numbers of patients with locoregional recurrence and locoregional progression in the thyroid bed or regional lymph nodes will be summarized using descriptive statistics.
- 16.232 Numbers of patients with distant metastasis will be summarized using descriptive statistics.

16.24 Correlative aims:

- 16.241 To evaluate the evolution of the immune profile of circulating immune cells in response to therapy in ATC patents, and to assess potential correlations with outcomes on an exploratory basis. For the immune profile, a plot of the fold change versus response status will be constructed to visually assess differences between those whose tumor responded to treatment and those whose tumor did not. Wilcoxon rank sum tests will be used to examine whether fold changes in a given immune profile differs between those whose tumor responded to treatment and those whose tumor did not.
- 16.242 To determine if pre-therapy circulating tumor cell load might predict response and recurrence. Wilcoxon rank sum tests will be used to examine whether the pre-therapy circulating tumor cell load differs between those whose tumor responded to treatment and those whose tumor did not, and between those who had recurrence versus who did not.
- 16.242 To evaluate ATC PD-1 and PDL-1 staining in tumor cells and tumor stroma as candidate biomarkers for prognostic and/or response in ATC. Wilcoxon rank sum tests will be used to examine whether PD-1 and PD L-1 staining differs between those whose tumor responded to treatment and those whose tumor did not.
- 16.242 To examine associations between tumor response and somatic mutational status in archived tumors, a 95% confidence interval for the difference in proportion of patients who have a documented tumor response among those with that particular biomarker present and proportion of patients who have a documented tumor response among those without that particular biomarker present.

16.3 Reporting and Exclusions

16.31 Evaluation of adverse events.

All subjects will be evaluable for adverse events from the time of their first treatment with pembrolizumab.

16.32 Evaluation of response.

All subjects included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, Category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the subjects who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Subjects in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific. All conclusions should be based on all eligible subjects. Subanalyses may then be performed on the basis of a subset of subjects, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding subjects from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

16.4 Monitoring

The principal investigator and the study statistician will review the study periodically to identify accrual, toxicity, and any endpoint problems that might be developing. In addition, this study will be monitored according to the Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Plan that is currently in place. The MCCC Data Safety Monitoring Board (DSMB) is responsible for reviewing safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.41 Adverse Event Stopping Rules

NOTE: NCI CTCAE v4.0 will be used to determine grading for adverse event stopping rules. The AE stopping rule will be applied to patients in Cohorts A and B combined.

After first five patients are enrolled the enrollment will be suspended until all 5 patients complete chemoradiation. After the first 5 patients, if we see **three or more** patients **develop any immune-related adverse events attributed to the study drug** (“possible”, “probable” and “definite” only) **leading to permanent discontinuation of the chemoradiation** then further enrollment will be suspended.

NOTE: Autoimmune thyroiditis is allowed.

16.5 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the “ClinicalTrials.gov” website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.6 Subset Analyses for Minorities:

16.61 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.62 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	12	12	24
Ethnic Category: Total of all subjects	12	13	25
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	2	2
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	11	10	21
Racial Category: Total of all subjects	12	13	25

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino**Racial Categories:**

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Tissue Specimens to be collected for this Protocol

Type of tissue biospecimen to submit	Mandatory or Optional	When to submit	Block, Slides, Core, etc. (# of each to submit)	Reason for submission	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
All diagnostic slides from original biopsy	Mandatory at baseline <u>AND</u> at the time of surgery	At time of enrollment if available or biopsy at screening (Cohorts A&B) <u>AND</u> at time of surgery (Cohort A only)	20 charged slides 5 microns thick sections (x2 sections per slide)	Correlative studies for immune phenotyping	Yes	Refrigerated
FFPE tissue blocks with corresponding H&E, OR unstained slides with corresponding H&E, from original biopsy	Optional after chemo-radiation and at end of treatment	After chemo-radiation <u>AND</u> at end of treatment	1 block or 20 charged slides 5 microns thick sections (x2 sections per slide)	Correlative studies for immune phenotyping	Yes	Refrigerated
Fresh frozen tissue	Optional	At enrollment (Cohort B) and at time of surgery (Cohort A) or after chemo-radiation (both cohorts)	5-10 mm tissue piece obtained from either surgical specimen or core biopsy	Correlative studies for immune gene expression studies	Yes	Frozen

17.2 Diagnostic Slides from original tissue and from surgical resection

- 17.21 Original biopsy or cytological specimen - ALL diagnostic slides used to make the diagnosis of ATC and ALL slides from surgical resection if performed should be clearly labeled and. If the original slides cannot be released, slides from the same tumor biopsy block used to make the diagnosis are acceptable.

The following materials are mandatory (unless indicated otherwise) and required for shipment:

- All diagnostic slides from original biopsy or cytologic specimen
- Pathology Reporting Form
- Tissue Submission Form
- Surgical Pathology Report
- Operative Report (optional)

Note: Please include the patient study ID number on all materials listed above.

- 17.23 The diagnostic slide(s) must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, patient study ID number, and patient initials. Send to [REDACTED].

- 17.24 Verify that Section 1 of the appropriate Pathology Reporting Form is completed correctly.

17.3 Correlative Tissue Collection

- 17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue

- 17.321 Tissue blocks will be collected from ATCs collected during routine diagnostic and/or therapeutic procedures will be requested for correlative studies per Table 17.1. The baseline tissue for correlative studies is mandatory and the tissue submission after chemoradiation and end of treatment is optional.

We will collect 5 micron thick sections on 20 charged slides from formalin fixed paraffin embedded (FFPE) blocks for immunohistochemical studies. If no FFPE blocks are available, optional core biopsies for research specific testing as indicated above may be requested at baseline (prior to therapy) and as indicated in the above table.

Tissue blocks from core biopsies obtained as a result of optional requests from consented patients will be sent for processing into FFPE blocks to Histology Core (13th floor Hilton) and stored in co-PI's mentor's lab (Dr. Allan Dietz, 3rd floor Stable).

- 17.322 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, patient study ID number, and patient initials.

- 17.323 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the

Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet). A hard copy of the form must be submitted with the tissue.

- 17.324 Mayo Clinic Study Coordinator to obtain materials and work with study pathologist, Dr Michael Rivera, for review.

17.33 Frozen Tissue

- 17.331 Optional, research obtained core biopsies of ATC tissues pre and/or following initiation of pembrolizumab as indicated in the Table 17.1 above, will be portioned into 5-10 mm pieces that will be frozen for immune gene expression studies. Frozen tissue cassettes will be stored in co-PI mentor's lab of Dr. Allan Dietz, 3rd floor Stabile.
- 17.332 Please transport frozen tissue to Dr. Allan Dietz's laboratory, 3rd floor Stabile building
- 17.333 Store frozen tissue in liquid nitrogen or -70 degree Celsius freezer

17.4 Background and Methodology

ATCs have a high mutation burden, that when combined with chemoradiation, may lead to the elaboration of tumor neoantigens, thereby inducing susceptibility to anti-tumor immune responses following pembrolizumab therapy. Moreover, ATCs often develop from differentiated thyroid cancers (DTC), the latter of which are often associated, at least initially, with clinical and/or subclinical autoimmune thyroid disease (i.e. an anti-thyroid response). In DTCs, co-existent autoimmune thyroid disease, outcomes are generally favorable, suggesting an intact anti-thyroid/anti-tumor immune response. As DTCs progress to PDTC and ATCs, tumors become heavily infiltrated with TAMs that, together with acquired intrinsic tumor cell genetic alterations, promote an immune-suppressive tumor microenvironment that permits rapid tumor progression.

We hypothesize that the dynamic alterations in circulating and tumor infiltrating immune cell subtypes before and following chemoradiation plus pembrolizumab will inform clinical outcomes. This information will be used then as biomarkers to identify responders to pembrolizumab as well as to develop novel immune based combination strategies to overcome resistance among the non-responders.

17.41 Immunohistochemical studies

Immunohistochemical studies will be performed on FFPE sections pre and post pembrolizumab therapy to examine alterations in : 1) tumor infiltrating immune cells (i.e. T cells, TAMs, NK cells, DCs); 2) expression of MHC class expression proteins; 3) PD-1 and PD-L1 expression; 4) Ki67 proliferation index; and 5) apoptosis markers.

17.42 Gene expression studies

Alterations in tissue-derived immune signatures through gene expression studies will be evaluated during the course of therapy to identify immune phenotypes associated with tumor responses and/or those associated with resistance to therapies. For example, altered cytokine expression levels, may induce and/or impair anti-tumor immune responses which can be used to identify responders as well as to develop novel immune therapy combinations for non-responders.

17.43 Thyroid autoantibody screens

ATCs often develop from differentiated thyroid cancers (DTC), the latter of which are often associated, at least initially, with clinical and/or subclinical autoimmune thyroid disease (i.e. an anti-thyroid response). In DTCs co-existent with autoimmune thyroid disease, overall outcomes are reportedly favorable from limited studies, suggesting the presence of an intact anti-tumor immune response. As DTCs progress, however, to PDTC and ATCs, tumors become heavily infiltrated with TAMs, that together with acquired intrinsic tumor cell genetic alterations, promote an immunosuppressive tumor environment and tumor escape from host-mediated anti-tumor control. We hypothesize that development of anti-thyroid antibodies could predict the responders from non-responders when treated with pembrolizumab.

17.44 Circulating tumor cells

Circulating tumor cells load and decrease in their numbers have been shown to be prognostic markers in many cancers including breast (Cristofanilli, Budd et al. 2004; Liu, Shields et al. 2009; Smerage, Barlow et al. 2014) and thyroid cancer (Xu, Handy et al. 2016). However, data from ATC is lacking and we will aim to prospectively collect circulating tumor cells and correlate with outcomes. The RareCyte CTC technology is a comprehensive, reproducible and highly sensitive dual-platform for collecting, identifying and analyzing CTCs that does not rely on EpCAM expression for enrichment. (Campton, Ramirez et al. 2015). This platform allows for mechanically precise CTC retrieval, enabling the isolation of DNA derived from single or pooled CTCs for advanced genomic analyses including the detection of specific mutations and targeted NGS.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See [Section 4.0](#) and data submission table for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget

19.1 Costs charged to patient

Routine clinical care costs will be the responsibility of the patient and/or the patient's insurance company. This responsibility includes costs associated with surgery, radiation and with the administration of standard chemotherapy (doxorubicin and docetaxel). These drugs are commercially available and will be the responsibility of the patient and/or the patient's insurance company.

19.2 Tests to be research funded

- Correlative studies
- Pembrolizumab administration
- Collection, processing and storage of blood and tissue samples for future, unspecified research.

19.3 Other considerations

Pembrolizumab will be provided by Merck & Co.

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:

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

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II New York Heart Association Classification of Congestive Heart Failure

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while <i>at rest</i> . Mostly bedbound patients.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994. Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix III Radiation Therapy Quality Control Guidelines

1) Prescription dose and fractionation:

Total administered prescription dose: 66 Gy
Total number of fractions: 33

2) Target coverage

PTV6600 (photons) : $V_{100} \geq 95\%$ and max dose (0.03 cc) $\leq 110\%$

3) Normal tissue constraints

Spinal cord: Max dose (0.03 cc) ≤ 50 Gy

Parotid gland: mean dose to one of the parotid glands: ≤ 26 Gy

Oral cavity: mean dose ≤ 25 Gy

Submandibular glands: mean dose ≤ 39 Gy

Larynx: mean dose ≤ 60 Gy

Pharyngeal constrictors: mean dose ≤ 54 Gy

Esophagus: mean dose ≤ 34 Gy

Brachial plexus: maximum dose to 0.03 cc ≤ 60 Gy unless overlapping with CTV then ≤ 66 Gy

Lung: percentage of lungs receiving 20 Gy $\leq 20\%$

4) Treatment duration/interruptions

Elapsed days from first fraction to last fraction: ≤ 45 days

Treatment plans/administration meeting all of the above criteria will be considered “per protocol.”
Treatment plans/administration failing to meet one or more of the above criteria will be considered an “unacceptable deviation.”

Dose Specifications

Prescription dose shall be according to the following

PTV66 (CTV66 + 5 mm margin) will receive 66 Gy in 33 fractions at 2 Gy per fraction. PTV59.4 (CTV59.4 + 5 mm margin) will receive 59.4 Gy in 33 fractions at 1.8 Gy per fraction. All targets will be delivered simultaneously. Treatment will be delivered once daily, 5 fractions per week, over 6.5 weeks

The reported doses for PTV66 shall include the prescription dose as well as the maximum point dose (maximum dose encompassing 0.03 cc volume) for that PTV, % PTV receiving $\geq 93\%$, $\geq 110\%$ and $\geq 115\%$ of the prescription dose of that PTV, and the mean dose for that PTV.

All plans shall be normalized such that $\geq 95\%$ of the volume of PTV66 is covered by the 66 Gy isodose surface while more than $>95\%$ of the volume of PTV59.4 being covered by the 59.4 Gy isodose surface.

Technical Factors

External Beam Equipment and Beam Delivery Methods

Megavoltage equipment capable of delivering static intensity modulation a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy), including VMAT is required.

Treatment Planning, Imaging and Localization Requirements

The immobilization device should at least include the head, neck, and shoulders. It is strongly encouraged to use a customized head and neck rest, Precise Bite, and indexed hand grips.

Treatment planning CT scans will be required to define gross target volume(s), and clinical target volume(s). The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment.

All tissues, including entire lung volumes (both lungs), to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.2 cm slices through the region that contains the primary target volumes including the top of the treatment table superiorly and the entire lung volumes inferiorly.

The GTV and CTV, and normal tissues must be outlined on all CT slices in which the structures exist.

Treatment Planning/Target Volumes

The definition of volumes will be in accordance with the 1993 ICRU Report #50.

The Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, MRI, PET/CT, clinical information, and endoscopic findings. Grossly positive lymph nodes are defined as any lymph nodes >1 cm or nodes with a necrotic center. It is strongly encouraged that the radiation oncologist outlines the radiologic extent of the primary tumor and neck nodes along with a radiologist. Whenever possible, it is recommended that the diagnostic images be fused to the planning CT scan image dataset to more accurately define the GTV. To further subdivide the GTV, gross disease at the primary site is designated as GTV-P and clinically involved gross lymph nodes are designated GTV-N. In situations where the patient underwent surgery prior to radiation therapy, the GTV is defined as the preoperative gross disease plus the post-operative surgical bed.

The Clinical Target Volume (CTV): See the bulleted list below for delineation details.

For patients without complete surgical resection: In terms of the GTV (GTV-P and GTV-N), a margin of ≥ 10 mm should be given circumferentially around the GTV (GTV-P and GTV-N) and this volume will be called the CTV₆₆ (CTV₆₆-P and CTV₆₆-N).^{*} This margin can be reduced to as low as 1 mm for tumors in close proximity to critical structures, e.g., tumors next to the spinal cord. For regions deemed to be at high risk for microscopic disease, all potential routes of spread for primary and nodal GTVs should be delineated by the treating radiation oncologist. This is known as CTV for subclinical disease or CTV_{59.4}.^{*} CTVs will not include air or normal adjacent organs that have not been invaded (cartilage, bone, brachial plexus, etc.)

- For patients who have undergone a complete surgical resection: CTV₆₆ should include the preoperative gross disease at the primary disease site or any grossly involved lymph nodes as well as the post-operative bed. A CTV_{59.4} also can be delineated if the region is at risk for microscopic spread and the region has not had surgery.
- To further define the subclinical region at risk for microscopic spread at the primary disease site, CTV_{59.4}-P includes CTV₆₆-P + ≥ 5 mm margin and ensuring that the following is generously covered: tracheal-esophageal groove, levels II-VI, and upper mediastinal nodes to

the level of the carina. At the discretion of the treating physician, level I and the retropharyngeal nodes can be covered when indicated.

Note: The outer most boundary of CTV_{59.4-P} should be at least 15 mm from the GTV-P. Typically, it is larger as coverage of the regions defined above is necessary. In regions near the spinal cord, the margin can be as low as 1 mm.

- Regarding the lymph nodal subclinical regions, CTV_{59.4-N} includes, as stated above, levels II-VI bilaterally and the upper mediastinal nodes down to the level of the carina. At the discretion of the treating physician, level I and the retropharyngeal nodes can be covered when indicated.

Note: The outer most boundary of the CTV_{59.4-N} should be at least 10 mm away from the GTV-N. In regions near the spinal cord, the margin can be as small as 1 mm.

A separate Planning Target Volume (PTV) for photons will provide a margin around the CTVs to compensate for the variabilities of treatment set up and internal organ motion. 5 mm around the CTVs is required in all directions to define each respective PTV (PTV₆₆, PTV_{59.4}). Note that at any given point, the margin from the GTV at the primary site to the PTV_{59.4} should be at least 20mm. This also applies to post-operative cases. The only exception is when the tumor is close to the spinal cord where CTV margin may be reduced to 1 mm with the intent of protecting the spinal cord.

Planning

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs (photons) and critical normal structures. An “inverse” planning using computerized optimization should be used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissue.

Critical Structures

Note: Structures marked “required” in the table below must be contoured

New Standard Name	Description
GTV	Required
CTV_6600	Primary Tumor Bed plus involved nodes Required
CTV_5940	At risk regions Required
PTV_6600	CTV-PTV 5 mm margin Required
PTV_5940	CTV-PTV 5 mm margin Required
SpinalCord	Spinal Cord Required
SpinalCord_05	Planning risk Volume of 5 mm margin Required
Parotid_L	Left Parotid Required
Parotid_R	Right Parotid Required
OralCavity	Oral Cavity Required
BrachialPlexus_L Brachial Plexus_R	Brachial Plexus Required
Mandible	Mandible Required

New Standard Name	Description
Submandibula_L	Left Submandibular gland Contouring Optional
Submandibula_R	Right Submandibular gland Contouring Optional
Esophagus	Esophagus Required
Larynx	Larynx Required
External	External border of patient used to define Unspecified Tissue Required
Lungs Constrictors_P	Total lung Required Pharyngeal constrictors Required
NonPTV (photons)	Unspecified tissues outside PTV Required

Critical Normal Structures

Surrounding critical normal structures, including spinal cord, parotid glands, skin (in the region of the target volumes), oral cavity, mandible, brachial plexus, esophagus and larynx must be outlined.

Physicians should assist the planner in identifying the critical normal structures. A planning risk volume (PRV) is applied only to the true spinal cord. The spinal cord PRV will be defined as a three-dimensional margin of 5 mm. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.

DVHs must be generated for all critical normal structures, any corresponding PRVs, and the unspecified tissues.

The method used for tissue heterogeneity calculations shall be reported. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

Planning Priorities

Critical normal structure constraints followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order:

- 1) Spinal Cord Dose Constraints
- 2) Dose coverage to tumor volumes
- 3) Normal structure dose constraints for plan scoring
- 4) Other normal structures not used for plan score

Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Holidays and weekends are not considered treatment breaks. Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of life-threatening acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation. Treatment breaks should be made up by BID treatments (>6 hours between treatments) and/or weekend treatments so that the overall treatment time is unchanged.

Treatment plans will be scored as Per Protocol, Variation Acceptable, or Deviation Unacceptable. It is encouraged to generate treatment plans that fall within the dose limits defining the per protocol category (see tables below). For those target to critical structures geometries that are more challenging, some variation from the per protocol dose limits is acceptable. The variation acceptable dose limits are given in the table below. Plans that fall outside of the variation acceptable dose limits are scored as deviation unacceptable.

	Per Protocol	Variation Acceptable	Variation Unacceptable
PTV_6600			
Total RT dose to 95% of the PTV_6600	66 Gy	66 Gy - 62.7 Gy	<62.7 Gy
Percentage of PTV_6600 receiving 61.4 Gy (93% of 66 Gy)	≥99%	≥97%	≤97%
Percentage of PTV_6600 receiving 72.6 Gy (110% of 66Gy)	≤20%	≤40%	≥40%
Percentage of PTV_6600 receiving 75.9 Gy (115% of 66 Gy)	≤5%	<20%	≥20%
Mean dose of PTV_6600	≤70.4 Gy	70.4 -72.6 Gy	≥72.6 Gy
PTV_5940 (photons)			
Total RT dose to 95% of PTV_5940	59.4 Gy	59.4 -56.4 Gy	<56.4 Gy
Percentage PTV_5940 receiving 55.2 Gy (93% of 59.4 Gy)	≥99% Gy	≥97%	≤97%

Acceptable Dose Limits on Critical Structures for Plan Scoring

Critical Normal Tissue			
Maximum dose to 0.03 cc of SpinalCord	≤45 Gy	45 - 48 Gy	≥48 Gy
Maximum dose to 0.03 cc of SpinalCord_05	≤50 Gy	50-54 Gy	≥54 Gy
Mean dose to one of Parotid glands	≤26 Gy		
50% of one of the Parotid glands		≤30 Gy	≥30 Gy
20 cc of both parotids		≤20 Gy	≥20 Gy
Percentage of Lungs receiving 20 Gy	≤20%	≤25%	≥25%

Suggested Dose Limits Not for Plan Scoring (Should Not Compromise Tumor Volume Coverage)

Oral cavity (excluding PTVs)	Mean dose ≤25 Gy
Submandibular glands	Mean Dose ≤39 Gy
Larynx	Mean dose ≤60 Gy
Maximum dose to 1cc of un-specified Tissue	≤69.3 Gy
Maximum dose to 0.03cc of Brachial Plexus	≤60 Gy
Maximum dose to 0.03cc of Brachial Plexus when Tumor Volume is overlapped with Brachial Plexus	≤66 Gy
Esophagus	Mean ≤34 Gy
Pharyngeal constrictors	Mean ≤54 Gy

Appendix IV Pembrolizumab ECI Drug-Induced Liver Injury (DILI)

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function (Navarro and Senior 2006). Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products (Björnsson 2006). Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to postauthorization phases of the product life cycle (excerpted from Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010).

As stated in the United States Food and Drug Administration (FDA) Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g. aspirin, tacrine, statins, and heparin) as well as by drugs that do cause such injury. The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI, because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function accompanying or promptly following evidence of hepatocellular injury.

The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e. AT elevation) accompanied by jaundice (i.e. TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of subjects meeting the laboratory criteria for potential DILI defined as:

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
 - an elevated total bilirubin (TBL) lab value that is greater than or equal to two times (2X) ULN and
 - at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- as a result of within-protocol-specific testing or unscheduled testing.

The protocol identifies these laboratory criteria for potential DILI as ECIs. ECIs are selected adverse experiences that must be reported within 24 hours.

Initiate **close observation** as defined below and continue follow-up until resolution.

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant medication use (including prescription and nonprescription medications, herbal and other dietary supplements), alcohol use, recreational drug use and special diets. (See Section 5 for details.)
- Obtain a history of exposure to chemical agents or other environmental toxins.
- Obtain additional history and complete Stage 1 workup to attempt to rule out other potential causes of the transaminase elevation, including but not limited to the following: acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Consider gastroenterology or hepatology consultation

Appendix V Presentation of Dermatologic Event

Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience CRF. Any treatments administered should be entered in the medical record. **Scan and forward this form to Principal Investigator.**

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?

2. Has the subject contacted any known allergens? Yes No
If so what kind? _____
3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? Yes No
If so what kind? _____
4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? Yes No
If so what kind? _____
5. Has the subject consumed unaccustomed, special or unusual foods? Yes No
If so what kind? _____
6. Does the subject have or had in the last few days any illness? Yes No
If so what kind? _____
7. Has the subject come into contact with any family or house members who are ill?
 Yes No
If so what kind? _____
8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? Yes No
9. Has the subject had recent sun exposure? Yes No
10. For the current rash, have there been any systemic clinical signs? Yes No
If so what kind? _____
 - i. Anaphylaxis? Yes No
 - ii. Signs of hypotension? Yes No

iii. Signs of dyspnea? Yes No

iv. Fever, night sweats, chills? Yes No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? Yes No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? Yes No

List medication(s) and dose(s): _____

13. Is the rash pruritic (itchy)? Yes No

Focused Skin Examination

Focused Skin Examination:

Key information should be summarized and entered on the Adverse Experience CRF.

Primary Skin Lesions Description

Color: _____

General description:

Describe the distribution of skin reaction, skin eruption, or rash on the body:

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

Any associated signs on physical examination?

Scan this form and forward by email to the Principal Investigator listed on the cover page of the protocol.