Title: A Phase 2 study of Nivolumab plus Ipilimumab in RAI refractory, aggressive thyroid cancer with exploratory cohorts in medullary and anaplastic thyroid cancer

NCT Number: NCT03246958

IRB Approval Date: 12/21/2021

DF/HCC Protocol #: 17-255

Title:
A Phase 2 study of Nivolumab plus Ipilimumab in RAI refractory, aggressive thyroid cancer with exploratory cohorts in medullary and anaplastic thyroid cancer

Coordinating Center:
Dana-Farber Cancer Institute, Boston, MA 02215

Principal Investigator (PI):
Kartik Sehgal, MD
Dana-Farber Cancer Institute
450 Brookline Ave, D2-136
Boston MA 02115
Phone (617) 632-3090
Fax (617) 632-4448
kartik_sehgal@dfci.harvard.edu

Other Investigators:

Biostatistician:

Research Nurses:

Agents:
Nivolumab and Ipilimumab (Supplied by Bristol-Myers Squibb)

IND #:
134668

IND Sponsor:
Kartik Sehgal, MD

Protocol Version # / Version Date:
August 30, 2021

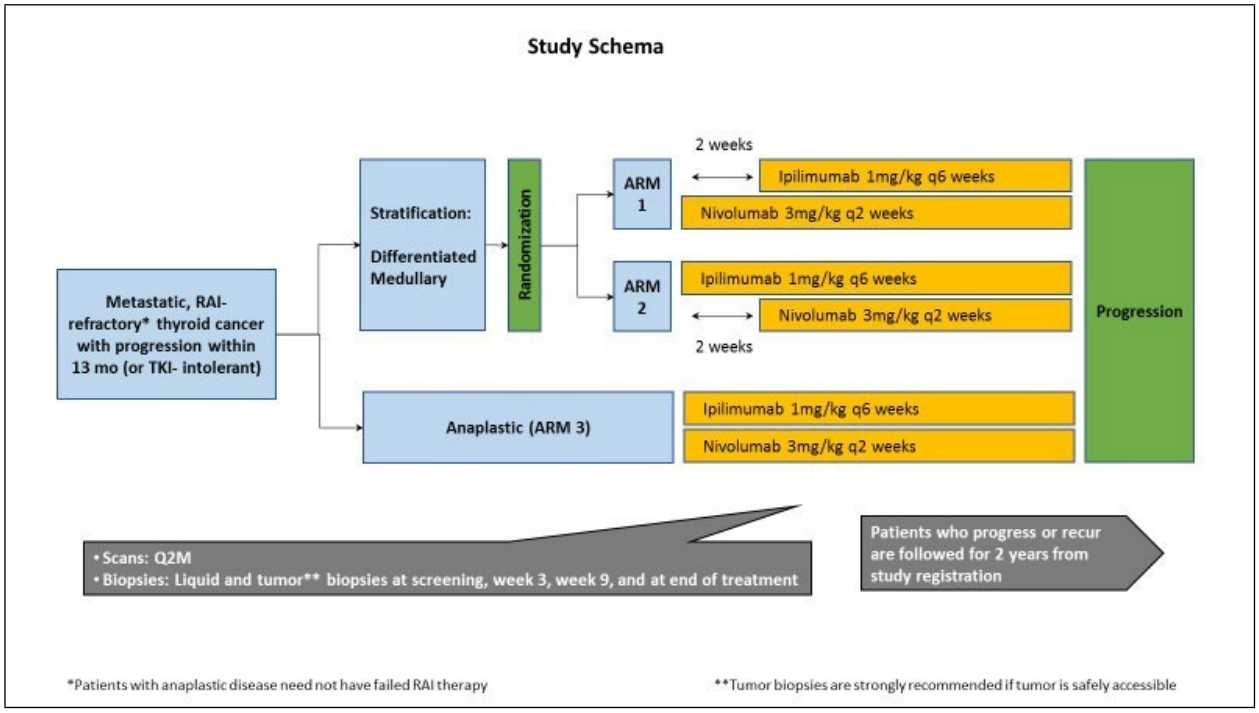
Study Schema
Metastatic, RAI-refractory* thyroid cancer with progression within 13 mo (or TKI- intolerant)
Stratification:
Differentiated
Medullary
Randomization
ARM 1
ARM 2
2 weeks
Ipilimumab 1mg/kg q6 weeks
Nivolumab 3mg/kg q2 weeks
Ipilimumab 1mg/kg q6 weeks
Nivolumab 3mg/kg q2 weeks
2 weeks
Anaplastic (ARM 3)
Ipilimumab 1mg/kg q6 weeks
Nivolumab 3mg/kg q2 weeks
Progression
• Scans: Q2M
• Biopsies: Liquid and tumor** biopsies at screening, week 3, week 9, and at end of treatment
Patients who progress or recur are followed for 2 years from study registration
*Patients with anaplastic disease need not have failed RAI therapy
**Tumor biopsies are strongly recommended if tumor is safely accessible

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a Phase 2 study with a randomized lead-in phase of nivolumab in combination with Ipilimumab in Radioactive iodine (RAI) refractory, aggressive thyroid cancer, with exploratory cohorts in medullary and anaplastic thyroid cancer. The medullary cohort will be randomized (along with patients with differentiated thyroid cancer), but in the anaplastic cohort, there will be no randomization. Due to the aggressive nature of anaplastic thyroid cancer, patients with anaplastic disease will receive nivolumab and ipilimumab at their first treatment.

The combination of nivolumab and ipilimumab was chosen because of mechanistic rationale, preclinical data and clinical evidence suggesting synergy between these two agents.

The goal of the study is to test the hypothesis that CTLA-4 and PD-1 inhibition combined is able to induce immunologic response in RAI refractory thyroid cancer resulting in tumor cell death and tumor shrinkage.

Patients will be seen at screening and then every 2 weeks during treatment until 24 months from first study treatment, or until treatment discontinuation. Basic lab values will be obtained at every visit. Scans of known areas of disease will be obtained every 2 months and evaluated by RECIST v1.1.

1.2 Primary Objectives

To evaluate efficacy in terms of the Radiographic Response Rate to the investigational treatment, as determined by RECIST v1.1 (PR+CR)

1.3 Secondary Objectives

To evaluate progression-free survival (PFS)
To evaluate overall survival (OS)
To evaluate tolerability
To explore biomarkers through correlatives

2. BACKGROUND

2.1 Study Disease

Thyroid cancer is the ninth most common cancer in the United States. In 2014, it was estimated that nearly 63,000 Americans will be diagnosed with thyroid cancer, and nearly 1,900 will die of the disease. The overall incidence of thyroid cancer in the United States has increased in people of all racial/ethnic groups and in both males and females over the past several decades.

Thyroid cancer incidence rates vary by both sex and race, with incidence being nearly three times higher in women than in men and nearly twice as high in whites as in African Americans. After whites, Asians/Pacific islanders have the second highest incidence. Overall mortality rates remain low despite rising incidence at an average of 0.8% annually from 2002-2011.

Differentiated Thyroid Cancer
DTC includes papillary and follicular thyroid cancer as well as poorly differentiated histologies. Most DTC cases are usually cured with surgery, radioactive iodine (RAI), and thyroid hormone suppression therapy. Papillary thyroid cancer (PTC) is the most frequent type of thyroid cancer. Most people who develop thyroid cancer are between age 25 and 65 years. The prognosis is generally good; however, 7–23% of patients, distant metastases develop and further treatment with RAI can eradicate the disease in only one third of such cases, while two thirds develop radioiodine refractory (RAIR) disease. The 10–year survival rate among patients with RAIR DTC is only 10% (1). Currently, only two multi-targeted tyrosine kinase inhibitors (TKI) have U.S. Food and Drug Administration (FDA) approval for progressive DTC based on improved PFS compared to placebo in two large phase 3 studies. Sorafenib demonstrated a 5-month improvement in median PFS versus placebo (10.8 versus 5.8 months) in a phase 3 trial of 447 RAIR TC patients who had progressed within 14 months prior to enrollment (2). Lenvatinib, also demonstrated a significant improvement in median PFS compared to placebo (18 months versus 3.6 months) in a phase 3 trial of 330 RAIR TC patients who had progressed in the prior 13 months (3). Remarkably, neither study showed a survival benefit for the patients on the experimental arm except for those age 65 and older (4). Crossover was allowed in these studies.

Recent data suggests that PD-1 and PD-L1 are over-expressed in thyroid cancer and the amount of PD-L1 expression appears to correlate with prognosis.

The PD-1 inhibitor pembrolizumab has been tested in a phase I study that included 22 patients with PD-L1 positive metastatic thyroid cancer (5). Eighteen of these patients had previously been treated with radioiodine and were considered RAI refractory. Two out of 22 patients had a partial response (9.3%).

The goal of this study is to determine response rate in patients with RAI refractory thyroid cancer that is incurable.

Medullary Thyroid Cancer
Medullary thyroid cancer constitutes approximately 2% of cases diagnosed with thyroid cancer and is derived from parafollicular C-cells. While it may not progress even as metastatic disease for many years, most patients enter an accelerated disease phase and require medical treatment. Tyrosine kinase inhibitors Vandetanib and Cabozantinib are FDA approved for this disease based on randomized phase 3 studies which showed a significant difference in PFS but no difference in overall survival. Subgroup analysis showed that this was true for all subgroups except for those who had the RET M918T mutation. In that group, survival was improved over placebo.

Pulsed dendritic cells were used in a study to treat refractory medullary thyroid cancer and decrease in tumor markers were seen suggesting that medullary thyroid cancer may be amenable

to immunotherapy. However, no published experience with modern immunotherapy drugs has been published in medullary thyroid cancer. Given the fact that, there are no established treatment options beyond first line treatment and frequently, once patients have entered the accelerated phase, the cancer is very aggressive and response to TKI treatment is often brief.

However, no published reports have demonstrated efficacy of PD-1 or CTLA-4 directed therapy has been published.

This study will include an exploratory cohort of 7 patients with medullary thyroid cancer with any number of prior therapies (including first line in this patient population without the RET M918T mutation) to explore possible use of IO in this patient population. Exploratory cohorts (histologic subtypes) will be randomized.

Anaplastic Thyroid Cancer
Anaplastic thyroid cancer constitutes approximately 1-2% of all thyroid cancer cases. It is usually a disease of the elderly with about three out of every four patients over the age of sixty and occurs more frequently in women than in men. It is one of the most aggressive solid tumors and is characterized by extremely aggressive growth and early metastasis. It accounts for 30-50% of thyroid cancer mortality and no effective standard of care exists for these patients (6). An unpublished study using the CTLA-4 inhibitor ipilimumab together with radiotherapy to the neck in anaplastic thyroid cancer also showed responses outside of the radiation field, suggesting systemic activity of this drug in thyroid cancer. Before initiating this protocol, we treated one patient with metastatic anaplastic thyroid cancer with the PD-1 inhibitor nivolumab and saw a mixed response with significant tumor shrinkage in several areas.

In Vitro Studies
Our own in vitro data suggests that ipilimumab and nivolumab may have significant activity in differentiated as well as aggressive thyroid cancer (Russell Jenkins and David Barbie, manuscript submitted). In this assay, tumor cells from thyroid cancer biopsies or pleural effusions were grown to spheroids in a 3-dimensional microfluidic fluid chamber system along with the tumor infiltrating immune cells from the same individual. Treatment of these spheroids with ipilimumab and with nivolumab resulted in impressive, unusually rapid cell death compared with other tumor types tested in this system while untreated spheroids continued to grow. Cytokine release measured in the culture media was suggestive of a specific T-cell mediated anti-tumor response.

These data and the lack of viable treatment options for this patient population are the basis for this study. The primary goal is to study the activity of this combination in incurable RAI refractory thyroid cancer but will also include exploratory cohorts in medullary and anaplastic thyroid cancer. Exploratory cohorts (histologic subtypes) will be randomized.

2.2 IND Agents

Nivolumab

Mechanism of action and pharmacology

Cancer immunotherapy is based on the premise that the body's immune system can recognize a tumor as foreign and mount an effective antitumor response capable of eliminating that tumor. This likely requires immune recognition of specific tumor antigens, but also effective functioning of activated T-cells capable of eliminating tumor cells as they arise and causing tumor shrinkage where existing tumor deposits are present. Conversely, tumor progression is likely intimately intertwined with mechanisms by which tumors evade immune recognition and attack.

One mechanism by which tumors may evade immune attack is by coopting inherent immune checkpoints that function under normal circumstances to maintain immune homeostasis and prevent harmful autoimmunity. Thus, one strategy that exists for cancer immunotherapy is to modulate these regulatory immune checkpoints that largely exist on the surface of T-cells. This can ideally overcome tumor mediated immune suppression, and potentiate nascent antitumor immune responses that might otherwise have been unable to lead to meaningful tumor regression.

Programmed death receptor-1 (PD-1, CD279), is a 55 kD type I transmembrane protein is a member of the CD28 family of T-cell costimulatory molecules that also includes CD28, CTLA-4, ICOS, and BTLA (7). PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273) (8). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems (8, 9). PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region (10, 11). PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells (11).

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus (12-14). The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes (15, 16). Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1 (17-22). This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans,

constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies (23-28). PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro (11). Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells (29). Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness (26, 27). Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared to low expression levels of PD-L1(30).

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro (31). Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-α release (32).

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at <=10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC (0-168 h)] 117,000 □g□□ h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy

failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice (33).

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, and clear-cell renal cell carcinoma (RCC) in addition to other tumor types. Please refer to the 2015 IB for specific details. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Nivolumab is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma, advanced renal cell carcinoma and previously treated, metastatic squamous NSCLC, the EU for treatment of previously treated, unresectable or metastatic melanoma, and Japan for treatment of unresectable melanoma.

On November 10, 2016, the U. S. Food and Drug Administration approved nivolumab (OPDIVO Injection, Bristol-Myers Squibb Company), for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy.

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials (please see 2015 IB for more details).

Clinical safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab+ipilimumab, as is proposed in this study. Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy, described in more detail below, is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

Safety data for nivolumab administered in the context of NSCLC and melanoma are detailed below; additional information for other diseases can be found in the IB.

Safety data for subjects with previously treated advanced or metastatic NSCLC treated with nivolumab monotherapy in CA209017 (131 subjects), CA209057 (287 subjects), and CA209063 (117 subjects) were pooled and safety analyses were performed for these pooled subjects who receiving nivolumab monotherapy (a total of 535 subjects).

Based on the pooled analyses, nivolumab monotherapy at a dose of 3 mg/kg administered IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The following were the key safety findings for these pooled subjects:

The most frequently reported drug-related AEs (reported in ≥ 10% of subjects) were fatigue (19.6%), decreased appetite (12.3%), nausea (12.0%), and asthenia (10.5%). The majority of drug-related AEs were of Grade 1-2 in severity. Drug-related Grade 3-4 AEs were observed in 11.0 % of subjects and included fatigue (1.7%), pneumonitis (1.3%), and diarrhea (0.9%).

Drug-related SAEs and drug-related AEs leading to discontinuation were reported in 7.9% and 6.0% of subjects, respectively. The most frequently reported event (>=1% of subjects) was pneumonitis (1.9%). The majority of subjects experiencing drug-related SAEs and drug-related AEs leading to discontinuation had an event with worst grade of Grade 3-4 in severity.

The most frequently reported drug-related select AE categories were skin (15.1%), GI (8.4%), and endocrine disorders (7.3%).

The majority of select AEs in each category (described in more detail in the IB) were considered by the investigator to be related to the study drug, except for AEs belonging to the hepatic, and renal select AE categories.

Across select AE categories, the majority of events were manageable, with resolution occurring whether or not immunosuppressive medication was needed. Among these medications, corticosteroids were the most common immunosuppressive concomitant medication administered.
Most deaths (293/339) were due to disease progression. Two deaths (0.4%) were attributed to study drug toxicity: drug-related hypoxic pneumonia reported within 30 days of last nivolumab dose (ie, on-study) and drug-related ischemic stroke within 100 days of last nivolumab dose. One additional death, although reported prior to database lock for CA209057 CSR, had its causality changed after database lock to drug-related paraneoplastic limbic encephalitis.

Hematology laboratory results, liver function, renal function, and thyroid function remained stable in the majority of subjects. Abnormalities were primarily Grade 1-2 in severity. The immunogenicity of nivolumab was low and not clinically meaningful.

Safety data for subjects with previously treated and untreated unresectable or metastatic melanoma treated with nivolumab monotherapy in CA209037 (268 subjects), CA209066 (206 subjects), and CA209067 (313 subjects) were pooled and safety analyses were performed for these pooled subjects receiving nivolumab monotherapy (a total of 787 subjects).

Based on the pooled analyses, nivolumab monotherapy at a dose of 3 mg/kg administered IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The following were the key safety findings for these pooled subjects:

The most frequently reported drug-related AEs (>=10% of subjects) were fatigue (29.2%), pruritus (18.4%), diarrhea (17.2%), rash (16.9%), and nausea (13.7%). No drug-related Grade 3-4 AEs with the exception of lipase increased (2.0%), diarrhea (1.3%), and ALT increased (1.1%) were reported in ≥ 1% of subjects.

No drug-related SAEs of any grade were reported in ≥ 1% of subjects. The most frequently reported drug-related SAEs of any grade were hyperglycemia (0.6%), colitis, diarrhea, and pneumonitis (0.5% each).

No drug-related AEs leading to discontinuation of study drug were reported in ≥ 1% of subjects. The most frequently reported drug-related AEs leading to discontinuation of study drug were ALT increased (0.9%), diarrhea (0.8%), AST increased (0.5%), and colitis (0.5%).

The most frequently reported drug-related select AE categories with nivolumab monotherapy were skin (38.4%), GI (17.7%), endocrine (10.8%), and hepatic (6.9%). The majority of select AEs were considered by the investigators to be related to study treatment.
Drug-related select AEs were mostly Grade 1-2.

Across categories, the majority of high-grade events subsequently resolved, including those for which immunosuppressive medication was not initiated.

The majority of deaths (229/251) were due to disease progression. Only 1 death was attributed to study drug toxicity; this death was due to drug-related neutropenia reported between 31 and 100 days of last nivolumab dose.

Abnormalities in select hematology assessments and liver/kidney function tests were primarily Grade 1-2 in severity.

The immunogenicity of nivolumab was low and not clinically meaningful.

Clinical Efficacy
Nivolumab has demonstrated efficacy across multiple tumor types including NSCLC, melanoma, renal cell carcinoma, esophageal cancer and most recently SCCHN. Approval for SCCHN was based on data from an international, multi-center, open-label, randomized trial (CheckMate 141) comparing nivolumab with investigator's choice (IC) of chemotherapy (either cetuximab, methotrexate, or docetaxel) in patients with recurrent or metastatic SCCHN with disease progression on or within 6 months of receiving platinum-based chemotherapy. Please see the IB version 15 for more details.

In subjects with previously treated, unresectable or metastatic NSQ NSCLC (CA209057), nivolumab monotherapy demonstrated superior OS compared with docetaxel, with a clinically meaningful and statistically significant improvement observed (HR=0.73 [95.92% CI: 0.59, 0.89]; stratified log-rank test p-value = 0.0015). In subjects with previously treated, unresectable or metastatic SQ NSCLC (CA209017), nivolumab monotherapy demonstrated superior OS compared with docetaxel, with a clinically meaningful and statistically significant improvement observed (HR=0.59 [96.85% CI: 0.43, 0.81]); stratified log-rank test p-value = 0.0002).

Results of secondary endpoints of ORR, DOR, and TTR further support the antitumor activity of nivolumab in both SQ and NSQ NSCLC subjects. In CA209057, PFS was not statistically different between treatment groups; however, while the median PFS favored docetaxel, the overall HR and 1-year PFS rate favored nivolumab, indicating the potential for long-term PFS benefit from nivolumab in a subset of subjects. In CA209017, nivolumab treatment resulted in a clinically meaningful and statistically significant improvement in PFS with a 38% reduction in the risk of progression as compared with docetaxel.

Nivolumab demonstrated superior OS compared with dacarbazine in previously untreated subjects with BRAF wild-type advanced (unresectable or metastatic) melanoma, with a clinically meaningful and statistically significant improvement observed (HR=0.42 [99.79% CI: 0.25,0.73]; p<0.0001). Results of secondary and exploratory endpoints of PFS, ORR, DOR, and TTR further support the robust and durable antitumor activity of nivolumab in this population.

Nivolumab combined with ipilimumab

Preclinical activity and data
Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity by activating a more robust anti-tumor immune response compared to either agent alone. In vitro combinations of nivolumab plus ipilimumab increase IFN-gamma

production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone (34).

Preclinically, a 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

Clinical safety of single agent of ipilimumab and pharmacology
Ipilimumab has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at15 ng/mL, whereas saturation was observed at approximately 0.1 µg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 µg/mL and 1 µg/mL, respectively.

Ipilimumab has a terminal half-life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes. The population PK of ipilimumab was studied with 785 subjects and demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from population PK analysis is consistent with that determined by PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days, and 7.47 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with increase in body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of

ipilimumab based on a weight normalized regimen. Additional details are provided in the Investigator Brochure.

Bristol-Myers Squibb (BMS) and Medarex, Inc. (MDX, acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, 2 completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively. Refer to the IB for additional details.

While the types of safety events observed in subjects receiving ipilimumab do not appear to change, even in combination with other anti-cancer agents, the proportion of subjects experiencing one type or another irAE may be impacted by the choice of combination partner. For example, skin and GI irAEs predominate in monotherapy studies. In MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) Grade 5. The most frequent adverse events of interest were rash (30%), pruritis (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%). Additional details on the safety profile of ipilimumab, including results from other clinical studies, are also available in the ipilimumab IB.

Yervoy TM (ipilimumab) has been approved for use in over 47 countries including the United States (US, Mar-2011), the European Union (EU, Jul-2011), and Australia (Jul-2011). Of note, ipilimumab will be given at a lower dose (1mg/kg) in this trial as compared to many previously conducted trials in order to reduce the rates of ipilimumab induced toxicity.

Clinical safety of nivolumab combined with ipilimumab
The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD.

In a Phase 1 study, CA209004, ascending doses of nivolumab were studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and

nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). The following DLTs were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 subject); in Cohort 2 - Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject) and in Cohort 3 - Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

Among the 53 patients in the concurrent-regimen group, adverse events of any grade, regardless of whether they were attributed to the therapy, were observed in 98% of patients. Treatment-related adverse events were observed in 93% of patients, with the most common events being rash (in 55% of patients), pruritus (in 47%), fatigue (in 38%), and diarrhea (in 34%). Grade 3 or 4 adverse events, regardless of attribution, were observed in 72% of patients, and grade 3 or 4 treatment-related events were noted in 53%, with the most common events being elevated levels of lipase (in 13% of patients), aspartate aminotransferase (in 13%), and alanine aminotransferase (in 11%). A total of 6 of 28 patients (21%) had grade 3 or 4 treatment related events that were dose-limiting. Serious adverse events related to the treatment were reported in 49% of patients in the concurrent regimen group. Common grade 3 or 4 selected adverse events that were related to the therapy included hepatic events (in 15% of patients), gastrointestinal events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were observed, a finding that is consistent with previous experience with monotherapy. A total of 11 patients (21%) discontinued therapy owing to treatment-related adverse events, no drug-related deaths were reported (35).

More recently, the results of a phase 3 trial comparing the combination of nivolumab and ipilimumab to either agent alone in metastatic melanoma were reported (36). Nivolumab was given at a dose of 1 mg / kg and ipilimumab was given at a dose of 3mg/kg every three weeks for a total a four cycles. After this, nivolumab was continued alone every two weeks. There were 314 patients enrolled on the treatment arm combining nivolumab and ipilimumab. Adverse events of any grade occurred in 95.5% of those in this group. The most common adverse events group were diarrhea (in 44.1% of patients), fatigue (in 35.1%), and pruritus (in 33.2%). The incidence of treatment-related adverse events of grade 3 or 4 was also higher in the nivolumab plus-ipilimumab group (55.0%) than in the nivolumab group (16.3%) or the ipilimumab group (27.3%). Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred in 7.7% of the patients in the nivolumab group, 36.4% of those in the nivolumab-plus ipilimumab group, and 14.8% of those in the ipilimumab group, with the most common events being diarrhea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively). One death due to toxic effects of the study drug was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest), but none were reported in the nivolumab-plus-ipilimumab group.

Preliminary experience in lung cancer as part of the Checkmate-012 study has evaluated the combination of nivolumab and ipilimumab in patients with advanced non-small cell lung cancer. Preliminary data was presented at the 2015 World Conference on Lung Cancer. Four administration/dosing schedules for the combination of nivolumab and ipilimumab were

explored. In arm A, both agents were administered at a dose of 1 mg/kg every 3 weeks (Q3W, N = 31). In arm B, nivolumab was administered at 1 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W; N = 40). Arm C and D dosed nivolumab at 3 mg/kg Q2W and ipilimumab 1 mg/kg every 12 weeks (Q12W; N=38) or Q6W (N = 39). Treatment-emergent grade 3/4 adverse AEs occurred in 28% to 35% of patients in each group but led to discontinuation in just 3% to 10% of cases. All grade treatment-related AEs occurred in 77%, 73%, 74%, and 69% of patients in groups A, B, C, and D, respectively. The safety profile was consistent with previous studies of the combination, and the discontinuation rate associated with AEs was similar to rates observed with nivolumab alone. The only grade 3/4 adverse events that occurred in as many as 10% of patients were hepatic in arm B (10%) and skin-related in arm C and D (13%). Grade 3/4 pulmonary AEs occurred in no more than 3% of patients in any of the groups. There were no treatment-related deaths in the trial.

This data suggests that delivering fewer doses of ipilimumab at a lower dose of 1mg/kg will reduce the toxicity of this agent combined with nivolumab.

Clinical efficacy of nivolumab combined with ipilimumab
The combination of nivolumab and ipilimumab has been studied most extensively in melanoma, where combination therapy is now FDA approved.

In the Phase 1 study CA209004, ascending doses of nivolumab were studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm of this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n=14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a that evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). In the concurrent-regimen cohorts, across all dose levels, confirmed objective responses according to modified WHO criteria were observed in 21 of 52 patients (40%; 95% confidence interval [CI], 27 to 55) who had a response that could be evaluated. In addition, 4 patients had an objective response according to immune-related response criteria and 2 had an unconfirmed partial response. These patients were not included in the calculation of objective response rates.

After noting that several patients had major responses (approaching complete response), a post hoc analysis of the number of patients with tumor reduction of 80% or more was conducted. This depth of response was uncommon in published studies of checkpoint blockade (37). A total of 16 patients had tumor reduction of 80% or more at 12 weeks, including 5 with a complete response. In the concurrent-regimen group, overall evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for >24 weeks) was observed in 65% of patients (95% CI, 51 to 78). Responses were ongoing in 19 of 21 patients who had a response, with the duration ranging from 6.1 to 72.1 weeks at the time of data analysis (35).

More recently, the results of a phase 3 trial comparing the combination of nivolumab and ipilimumab to either agent alone in metastatic melanoma were reported (36). Nivolumab was

given at a dose of 1 mg / kg and ipilimumab was given at a dose of 3mg/kg every three weeks for a total a four cycles. After this, nivolumab was continued alone every two weeks. The median progression-free survival was 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab-plus-ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer progression-free survival was observed in the nivolumab plus-ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and in the nivolumab group than in the ipilimumab group (hazard ratio, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001).

The tumor-burden change was assessed as the change from baseline in the sum of the longest diameters of the target tumor lesions. The median change was −34.5% (interquartile range, −75.4 to 15.4) in the nivolumab group, −51.9% (interquartile range, −75.8 to −10.2) in the nivolumab plus-ipilimumab group, and 5.9% (interquartile range, −28.0 to 33.3) in the ipilimumab group.

Preliminary experience in lung cancer as part of the Checkmate-012 study has evaluated the combination of nivolumab and ipilimumab in patients with advanced non-small cell lung cancer. Preliminary data was presented at the 2015 World Conference on Lung Cancer. Four administration/dosing schedules for the combination of nivolumab and ipilimumab were explored. In arm A, both agents were administered at a dose of 1 mg/kg every 3 weeks (Q3W, N = 31). In arm B, nivolumab was administered at 1 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W; N = 40). Arm C and D dosed nivolumab at 3 mg/kg Q2W and ipilimumab 1 mg/kg every 12 weeks (Q12W; N=38) or Q6W (N = 39). All four regimens demonstrated activity, with the arms containing nivolumab at 3 mg/kg showing the best objective response rate (ORR). In arm C, the ORR was 39% and in arm D the ORR was 31%. The ORRs were 25% and 13%, in arm B and arm A, respectively.

2.3 Rationale

Immune checkpoint inhibitors are quickly becoming standard of care treatment options in many solid tumor types. In particular, PD-1, PDL-1 and CTLA-4 inhibition are now established therapies in Melanoma and have shown activity in most tumors tested.

Thyroid cancer is the most common endocrine malignancy worldwide and accounts for over 30 000 cases per year in the US. Multimodality treatment including surgery and radioactive iodine (RAI) results in a cure in >90% of differentiated thyroid cancer cases (DTC), which include papillary, follicular and poorly differentiated histologies with their respective sub-types. However, in approximately 10% of cases distant metastasis occurs and the disease becomes iodine refractory (RAI refractory), rendering it incurable. Sorafenib and lenvatinib are FDA approved for RAI refractory differentiated thyroid cancer based on randomized phase 3 studies which showed superior progression free survival compared to placebo but no difference in overall survival (OS) except for patients older than 65y (2, 4). We have tested mTOR inhibition with everolimus in a phase 2 study and found that the drug is very active in this disease as well (38). Everolimus will likely receive compendia listing this year based on our data. Medullary thyroid cancer which is derived from parafollicular c-cells, does not respond to RAI and has a 5 year survival of approximately 80%. The vast majority of these cases are driven by activating

RET mutations. Cabozantinib and vandetanib are FDA approved based on phase 3 studies which demonstrated differences in PFS but not OS. Anaplastic thyroid cancer is one of the most aggressive known malignancies known with a median survival of only approximately 6 months and 5 year survival less than 10%. For anaplastic thyroid cancer, no standard of care exists, although lenvatinib and mTOR inhibitors such as everolimus have shown promise (39).

Data are emerging about checkpoint inhibition in thyroid cancer. PD-1 and PD-L1 expression has been documented and expression appears to be more pronounced in more advanced cases (Han and Walfish, ATA 2015). If the BRAF V600E mutation is present, which occurs in approximately 60% of newly diagnosed cases of DTC, PDL-1 expression and tumor infiltrating lymphocytes appear to be higher than in BRAF-V600E no-mutated (WT) cases (40). Pembrolizumab, was tested in extensive phase 1 studies which included a number of RAI refractory thyroid cancer cases and PR's occurred in 2/22 (9%) cases that were PD-L1 positive. These data were presented at the annual ASCO meeting 2016.

The lack of predictive markers that could be used to select patients is a challenge in immunotherapy research. The correlation between PD-1 and PDL-1 expression and response to checkpoint inhibition is weak and of limited clinical usefulness in many tumor types. Traditional cell culture and tumor transplant models do not reflect the immune microenvironment and are also not considered reliable to predict tumor response in vivo.

Scientists at MIT and Dana Farber have developed a unique microfluidic chamber which allows the growth of tumor spheroids while preserving the full array of tumor invading immune cells. We have found that spheroids grown from 3 patients with RAI refractory thyroid cancer (2 RAI refractory papillary TC, one Hurthle cell follicular TC) showed mild response to PD-1 inhibition but a dramatic and very rapid response to CTLA-4 inhibition. Cytokine measurements in the cell culture fluid showed a rise in TNF-alpha, IL6, IFN gamma and IL2, all indicating response to checkpoint inhibition with CTLA-4 which closely resembles what would be expected in vivo (41). Of note, all patients had recently or currently been treated with mTOR inhibitors.

We recently treated a patient with anaplastic thyroid cancer off label with nivolumab and saw a mixed response with some lesions growing while others were getting smaller.

At this point, no standard options exist for patients with RAI refractory thyroid cancer or medullary thyroid cancer beyond first line treatment. Since none of the treatments available are curative and induce responses for limited time only, there is a major unmet need for treatment options.

Rationale for 24 Months Maximum Treatment Duration

The optimal duration of treatment by checkpoint blockade inhibitors in oncology is currently unknown. However, given their mechanism of action continuous treatment may not be required as opposed to targeted agents or most of cytotoxic therapies.

With almost a decade of experience using CTLA-4 and PD-1/PD-L1 inhibitors, accumulating evidence from different clinical trials in different tumor types indicates that most of the

responses are generally occurring early, with a median time to response of 2 to 4 months including in patients with NSCLC, and most of the responses are likely to be durable as compared to conventional therapies.

Limited duration of therapy was explored in few trials, for instance, ipilimumab the first checkpoint blockade inhibitor targeting CTLA-4 was initially approved in metastatic melanoma in participants who failed standard of care chemotherapy. This approval was based on overall survival improvement after a limited duration of ipilimumab therapy, including only 4 induction doses for a duration of treatment of 12 weeks, with a sustained plateau in survival starting at around year two. Moreover, in Checkmate 003 a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with advanced solid tumors implemented stopping nivolumab monotherapy at 96 weeks (~ 2 years). At 2 years, 16 NSCLC participants who were on still on therapy discontinued nivolumab per protocol, of these, 75% of patients (n = 12) were alive > 5 years and did not receive further therapy after stopping nivolumab and remained progression free.

Moreover, long-term follow up data from study KeyNote-006 a phase 3 Melanoma study demonstrates that pembrolizumab provides durable efficacy after stopping the protocol-specified duration of treatment at 2 years. The median follow-up was of 33.9 months, among the 104 (19%) participants who completed pembrolizumab, median exposure was 24.0 months. After additional median follow-up of 9.0 months after completion of pembrolizumab, 102 (98%) pts were alive and responses were durable in pts who completed pembrolizumab.

In addition, data from different series are showing that patients receiving immunotherapy-based treatment may discontinue treatment due to safety events. In a recent analysis in a melanoma study the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.

CheckMate 153 is the first randomized study to evaluate treatment duration with a PD-1/PD-L1 inhibitor. In this study, progression free survival appears to be durable with a plateau at 2 years from first dose including in pts who stopped nivolumab after 1 year, suggesting the risk of progression after 2 years of treatment is minimal, even in the absence of further treatment, which is consistent with existing data with PD-1/PD-L1 datasets. In addition, 34 out of 87 patients with clinical benefit who stopped therapy at 1 year were retreated upon progression as per protocol, in this group, nivolumab retreatment did not appear to re-induce responses and in the majority of the cases, the tumor continues to progress suggesting that treatment change, using preferentially an agent or approach with a different MOA.

Collectively, these data suggest that there is likely no benefit from treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be exposed to the risk of additional toxicity with longer-term treatment. Therefore, in CA209-651 treatment with nivolumab +/- ipilimumab will be given for up to 2 years from start of treatment.

2.4 Correlative Studies Background

Correlative studies are an integral part of this protocol to gain insight into the basic biologic

response to PD-1 and CTLA-4 blockade in thyroid cancer and the early identification of mechanisms of drug resistance. The purpose of the randomized lead-in phase with Nivolumab and ipilimumab starting sequentially is to provide opportunities to study the specific immunologic changes that occur in response to either drug alone as well as both drugs in combination. The clinical endpoints are assessed during treatment with both drugs combined.

Recently, a novel method for evaluating ex vivo response to immune checkpoint blockade using patient-derived organotypic tumor spheroids (PDOTS) cultured in a 3-dimensional microfluidic system has been developed. It could be demonstrated that spheroids isolated from fresh human tumor samples retain autologous lymphoid and myeloid cell populations, including antigen-experienced tumor infiltrating CD4/CD8 T lymphocytes, and survive in extracellular matrix. PD-1 and CTLA-4 blockade inhibition across a large panel of PDOTS including samples from 4 thyroid cancer patients consistently showed up-regulated homeostatic lymphokines involved in T- and B- cell chemoattraction, demonstrating the feasibility of ex vivo profiling of PD-1 and CTLA-4 blockade, it could also be demonstrated that induction of a dysfunctional cytokine response may contribute to intrinsic resistance. (Jenkins *et al*., *Nature*, under review).

We have tested samples from 4 patients with thyroid cancer and found that treatment of spheroid cultures with CTLA4, and to a lesser extent with PD-1 blockade led to the rapid cell death of thyroid cancer cells. These studies along with early reports to PD-1 and CTLA-4 blockade are the basis for this protocol.

Patients will be required to undergo sequential biopsies, if accessible tumor is present. Tumor samples will be grown in the microfluidic chamber system and tumor infiltrating lymphoid and myeloid cells will be analyzed both in vitro and by flow cytometry across several samples obtained prior to treatment, during treatment with nivolumab or ipilimumab and with both drugs combined. This will allow us to determine optimal sequencing of the 2 drugs, and potential mechanisms of resistance during treatment.

Circulating tumor cells (CTCs) may reflect the ongoing molecular evolution of thyroid cancer cells and reveal molecular and genetic changes that confer migration and invasion advantages. It is essential to define mechanisms of resistance at more than one timepoint. This is important because resistance mechanisms may be completely different at different stages of disease, but difficult to achieve with tissue biopsies. The goal of this exploratory endpoint is to understand how tumor heterogeneity evolves during progression of thyroid cancer, and with development of resistance/refractory disease. The objective is to determine the transcriptional profile of CTCs, myeloid and lymphoid WBC's in peripheral blood and compare to cancer and tumor infiltrating lymphoid and myeloid cells in tissue biopsies through RNA sequencing, and to define how these change with therapeutic intervention over time. Recent advances in next-generation sequencing and single cell isolation techniques will make this a minimally invasive approach to perform comprehensive genomics in patients with thyroid cancer to inform clinical treatment decisions.

In addition to CTCs, other circulating biomarkers can be detected in plasma and serum, such as cell-freeDNA (cfDNA), microvesicles and exosomes. Some of these markers have been found to correlate with increasing tumor burden and treatment response in various types of malignancies. cfDNA, and nucleic acids in microvesicles and exosomes in cancer subjects can harbor many

genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, blood may be a useful surrogate for tissue, and can be especially valuable at time points or in disease settings where tumor tissue collection may be challenging to evaluate drug response, resistance and disease progression.

In addition, cell sorting of peripheral CD4 and CD8 positive cells by flow cytometry and single cell sequencing provides an opportunity to evaluate the changes immune cells undergo in response to checkpoint inhibition with PD-1 and CTLA-4. Samples will be assessed for expression of markers of exhaustion (PD-1, CTLA-4, TIM3) and how these markers change in response to nivolumab, Ipilimumab or both drugs combined.
We have tested several peripheral blood samples from thyroid cancer patients and could document the presence of CTC's as well as cfDNA in approximately 60% of cases.

3. PARTICIPANT SELECTION

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

3.1 Inclusion Criteria

1. Metastatic, RAI-refractory, differentiated thyroid cancer (including papillary and follicular thyroid cancer and their sub-types such as Hurthle cell thyroid cancer as well as poorly differentiated thyroid cancer), medullary thyroid cancer, or anaplastic thyroid cancer. RAI-refractoriness is not required for medullary or anaplastic thyroid cancer patients. Patients who are not candidates for RAI therapy, as determined by the investigator, are also eligible.

   RAI-refractoriness is defined as absence of uptake of RAI on either a low-dose diagnostic test or a post-treatment RAI scan in measurable lesions or radiographic progression of disease within 12 months of the last course of RAI treatment despite the recorded uptake of RAI with that previous therapy or having a cumulative lifetime administered dose of greater than 600mCi.

2. Patients must have experienced disease progression within 13 months prior to study registration, have experienced intolerable side effects on a tyrosine kinase inhibitor (TKI), or be not suitable candidates for TKI. No progression is required for patients with anaplastic thyroid cancer.

3. Age 18 years or older

4. Any number of prior treatments allowed for patients under 65y, over 65y, if suitable candidate for TKI therapy, must have at least one prior line of TKI treatment (excluding medullary and anaplastic patients)

5. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

   Measurable disease by per RECIST 1.1 criteria (see section 11). Radiographic tumor assessment performed within 28 days of registration

6. Participants must have normal organ and marrow function as defined below:
   Screening laboratory values must meet the following criteria and should be obtained within 21 days prior to randomization/registration
   - WBC ≥ 2000/μL
   - Neutrophils ≥ 1200/μL
   - Platelets ≥ 100 x10^3/μL
   - Hemoglobin > 8.0 g/dL
   - Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

     $$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

     $$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$
   - AST/ALT ≤ 3 x ULN
   - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

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

8. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug

9. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 iu/l or equivalent units of hcg) at screening. Pregnancy test will be repeated on the day of the first dose of study drug (before administration), although results of this test are not required for registration.

   "Women of childbearing potential" is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

10. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product Women who are not of childbearing

potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception

3.2 Exclusion Criteria

1. Patients should be excluded if they have an active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger

2. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

3. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

4. As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.

5. Patients who have had chemotherapy/radiotherapy and/or targeted agentswithin 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. For patients with anaplastic thyroid cancer or otherwise particularly aggressive disease (as determined by the investigator), the washout period for chemotherapy/radiotherapy and/or targeted agents will be at the investigator's discretion.

6. Patients who are receiving any other investigational agents.

7. Patients with active brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

8. 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.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

For DTC and MTC patients, the eligibility checklist and all pages of the consent form will be faxed to the ODQ . The ODQ Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

For ATC patients, who will not undergo randomization, the study team is responsible for registering patients in OnCore.

An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101) must be followed.

4.3 Registration Process for Participating Sites

See Appendix E

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment will be administered on an outpatient basis. Expected toxicities and potential risk as well as management of these toxicities are described in Appendix B and Investigator's Brochures and/or Package Inserts. No investigational or commercial agents or therapies other than those

described below may be administered with the intent to treat the participant's malignancy during the course of treatment.

The treatment plan is shown below:

Nivolumab infusion at a dose of 3mg/kg, once every 2 weeks, until treatment discontinuation.
Ipilimumab infusion at a dose of 1mg/kg, once every 6 weeks, until treatment discontinuation.

For DTC and MTC patients, there will be randomization to 2 arms for a lead-in phase in this study:

Arm 1: Nivolumab starts 2 weeks prior to Ipilimumab
Arm 2: Ipilimumab starts 2 weeks prior to Nivolumab

The following stratification factor will be used in order to prevent imbalance across treatment arms:

- Histology (differentiated thyroid cancer vs. medullary thyroid cancer)

Infusion schedule Arm 1: Same schedule will be followed beyond week 17 until 24 months from first study treatment, or until treatment discontinuation.

	Wk1	Wk3	Wk5	Wk7	Wk9	Wk11	Wk13	Wk15	Wk17
Nivolumab	X	X	X	X	X	X	X	X	X
Ipilimumab		X			X			X	

Infusion schedule Arm 2: Same schedule will be followed beyond week 17 until 24 months from first study treatment, or until treatment discontinuation.

	Wk1	Wk3	Wk5	Wk7	Wk9	Wk11	Wk13	Wk15	Wk17
Ipilimumab	X			X			X		
Nivolumab		X	X	X	X	X	X	X	X

No difference in efficacy between the 2 arms is expected and endpoint analysis will be performed based on both arms combined.

Due to the aggressive nature of their disease, for patients with anaplastic thyroid cancer, both drugs will start synchronously on day 1. No randomization or lead-in phase will occur for these patients.

Infusion schedule Arm 3: Same schedule will be followed beyond week 17 until 24 months from first study treatment, or until treatment discontinuation.

	Wk1	Wk3	Wk5	Wk7	Wk9	Wk11	Wk13	Wk15	Wk17
Ipilimumab	X			X			X		
Nivolumab	X	X	X	X	X	X	X	X	X

This design will allow us to obtain liquid and in some cases tumor tissue biopsies sequentially that will provide valuable information about biological endpoints including changes in T cell invasion, release of inflammatory cytokines, cell death and RNA expression profile, cell free DNA, and circulating tumor cells at baseline, while on one drug alone, on both drugs and at the time of progression.

5.2 Pre-Treatment Criteria

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

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. If screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline cycle 1 day 1 visit and cycle 1 day 1 labs do not need to be performed.

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

Additional testing required, as per Section 3, is: hematology panel (see Table 1), chemistry panel (see Table 1), coagulation panel, urine or serum HCG (in women of childbearing potential; see Section 3 for when serum HCG testing is required), TSH (with reflexive Free T4 and Free T3), Mg, LDH, amylase, lipase.

Table 1: Clinical Laboratory tests.

Category	Tests
Hematology panel	
	• Hematocrit, hemoglobin, platelet count, WBC with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC
Chemistry Panel	
	• Chloride, potassium, sodium, BUN, serum creatinine, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, glucose

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; WBC = white blood cells

Archival tumor sample should be collected (block or if not possible, at least 20 unstained slides). If unavailable, a baseline tumor biopsy is required, if safe to perform.

5.3 On treatment visits

Reasonable effort should be made to conduct study visits on the day scheduled (+/- 3 days).

Any changes from screening clinical evaluation findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

If screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline cycle 1 day 1 visit and screening tests do not need to be repeated.

Pharmacy will follow the DFCI dosing weight practice which is to use the weight from baseline or the previous dose if it has not changed more than ≥ 5%.

5.4 Monitoring of Patients with Anaplastic Thyroid Cancer

Patients with anaplastic thyroid cancer have very aggressive disease and usually require immediate treatment. If a patient with anaplastic thyroid cancer chooses to participate, he/she will need to sign an additional section in the consent stating he/she agrees to weekly follow-up by phone or in clinic if he/she experiences intolerable symptoms, as determined based on an assessment by the patient's treating physician. Anaplastic thyroid cancer patients deemed to have intolerable symptoms will be followed closely outside of the protocol's study schedule (i.e., with phone calls or clinic visits to be determined by treating physician) until they achieve tolerable symptoms as assessed by the patient's treating physician.

5.5 Agent Administration

When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first. The second infusion will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion.

BMS-936558 (nivolumab) is to be administered as a 30 (+/- 15) minute IV infusion. Ipilimumab should be administered as a 30 (+/- 15) minute infusion following.

Ipilimumab and nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by ≥ 5% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram per institutional standard.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- A maximum of 24 months from the first study treatment

Participants will be removed from the protocol therapy when any of these criteria apply (with the exception of disease progression, in which case participants may or may not be removed from protocol therapy, at the investigator's discretion). The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy, Treatment Ended information will be updated in OnCore by the research team.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Kartik Sehgal, MD

5.6.1 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progression of disease (PD).

Subjects will be permitted to continue on study treatment for treatment beyond initial RECIST 1.1 defined PD up to a total of 24 months total treatment duration from the start of study treatment as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional study treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options. The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the investigator and documented in the study records.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar (section 10).

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

5.7 Duration of Follow Up

Participants will be followed for response until first disease progression or treatment discontinuation (whichever comes last) and for survival for 2 years from study registration. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and if have not experienced first disease progression at time of discontinuation of protocol therapy, will continue to be followed until first disease progression. After disease progression, patients will be followed by phone, until death or for 2 years from study registration (whichever occurs first).

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Patient completed required follow-up
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

The research team updates the relevant Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Reduction for Nivolumab and Ipilimumab:

There will be no dose reductions for nivolumab or ipilimumab permitted.

6.2 Dose Delay Criteria for Nivolumab and Ipilimumab:

Dose delay criteria apply for all drug-related AEs. Treatment delay is up to 6 weeks for nivolumab and up to 12 weeks for ipilimumab from the last dose are allowable (any dose delays greater than these will require approval from the PI).

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia does not require a dose delay
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range delay dosing for drug-related Grade ≥ 3 toxicity
    - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The PI should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
    - Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

- Subjects receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

Rescheduling:
- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 3 day window. Ipilimumab may be delayed beyond the 3 day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 6.4.

6.3 Treatment Discontinuation Criteria
For all subjects, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be captured on the health outcomes questionnaires. Tumor assessments for subjects who discontinue study treatment without radiographic progression, should continue as per protocol until radiographic progression is determined.

6.4 Nivolumab Dose Discontinuation
Treatment with nivolumab should be permanently discontinued for any of the following:
- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction regardless of duration;
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
- Any Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Any Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
- Any Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm, Appendix B):
  - AST or ALT > 5-10x ULN for > 2 weeks
    1. AST or ALT > 10x ULN
    2. Total bilirubin > 5 x ULN
    3. Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  1. Grade 4 neutropenia ≤ 7 days
  2. Grade 4 lymphopenia or leukopenia
  3. Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The PI should be consulted for Grade 4 amylase or lipase abnormalities
  4. Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the PI. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study.

6.5 Ipilimumab Dose Discontinuation

Ipilimumab should be permanently discontinued if any of the following criteria are met:

- Any Grade ≥ 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;

- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse event with the following exceptions for laboratory abnormalities, grade 3 nausea and vomiting, grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 8x ULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia □ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis. The PI should be consulted for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug related reasons may be allowed if approved by the PI. Prior to reinitiating treatment in a subject with a dosing delay lasting > 12 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued ipilimumab dosing

  The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

  If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

6.6 Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to

Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 6.7) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the PI.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≥ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The PI should be consulted prior to resuming nivolumab in such subjects.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 6.7.

6.7 Criteria to Resume Ipilimumab Dosing

Subjects may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (given below) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the PI.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted below.
- Ipilimumab may not be resumed sooner than 6 weeks (± 5days) after the prior ipilimumab dose.

- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- One exception to note is when ipilimumab and nivolumab doses are delayed due to drug related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the subject's medical chart. The PI should be consulted prior to resuming nivolumab in such subjects.

Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following

prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6.7.1 **Management Algorithms for Immuno-Oncology Agents**

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological.

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

The recommendations are to follow the algorithms in the nivolumab investigator brochure for immune related events; while the ipilimumab investigator brochure contains similar algorithms, the algorithms in the nivolumab brochure have been aligned to accommodate combinations as well as nivolumab monotherapy.

Therefore, the algorithms recommended for utilization are in Appendix B for reference.

Additional details on the safety of nivolumab and ipilimumab, including results from clinical studies, are available in the IB.

6.8 Concomitant Treatments

6.8.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in section 6.8.2)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer)
- Surgical resection of tumor

Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with nivolumab and/or ipilimumab. Discontinuation of the use of herbal medications prior to study enrollment is encouraged. Except for the permitted procedures specified as palliative local therapies (Section 6.8.3), all other radiation therapy or surgery to any tumor lesion is not permitted during study treatment. Subjects who require such non-palliative procedures must be discontinued from study treatment.

6.8.2 Other Restrictions and Precautions

Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

It is the local imaging facility ' s responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. If CT is contraindicated for a subject because of an iodinated contrast allergy, then a contrast enhanced MRI of the neck, chest, abdomen and pelvis will be performed. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

6.8.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Regular

concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in subjects with bone metastases is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 4 weeks prior to treatment.

For patients with differentiated or medullary disease, prior palliative radiotherapy must have been completed at least 8 weeks prior to randomization for cases of radiotherapy to the head and neck, and completed within 4 weeks prior to randomization for radiotherapy to other sites. On study palliative radiotherapy is only allowed for treatment of painful bone lesions. Palliative surgical resection of tumor sites is not permitted. Subjects requiring palliative radiotherapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST 1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression in order to resume immunotherapy after palliative local therapy.

Due to the aggressive nature of their disease, anaplastic thyroid cancer patients may receive palliative radiation to non-bone sites and/or resection at the investigator's discretion. For these patients, the washout period for radiation will be at the investigator's discretion.

The potential for overlapping toxicities with radiotherapy and nivolumab/ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab/ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab/ipilimumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade <=1 prior to resuming nivolumab or nivolumab plus ipilimumab.

6.9 Holding Study Treatment

Following disease control (i.e., stable disease or response) sustained over the course of a year or more of therapy (or as determined by the investigator), the investigator may decide to hold study treatment for an extended period of time. In this case, imaging will be continued with timing at investigator's discretion. The investigator may choose to restart study treatment based on scan results.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

7.1 Adverse Event Characteristics

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

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

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

7.2 Unanticipated/Life-Threatening Problems

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

7.3 Multi-Center Trial Requirements

Each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4 DF/HCC Adverse Event Reporting Guidelines

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

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

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

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

7.5 Expected Toxicities

Expected adverse events are those that have been previously identified as resulting from administration of the agent. Consistent with the mechanism of action of nivolumab and ipilimumab, the most frequently reported drug-related adverse events observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated adverse events include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. In the combination regimen, the frequency and intensity of these events may vary and depend on the specific dose and schedule used.

Management of these expected toxicities are described in Appendix B.

Please refer to the Investigator's Brochures and/or Package Inserts for more information on adverse events related to the study drugs.

7.6 Routine Adverse Event Reporting

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

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

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

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

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

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

7.7 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The

investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

7.8 Expedited Adverse Event Reporting to Overall PI

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

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

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

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

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

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH

7.10 Expedited Adverse Event Reporting to Hospital Risk Management

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

7.11 Expedited Adverse Event Reporting to BMS

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator. Sponsor/investigator will request a reconciliation report from: . During reconciliation, any events found to not be reported previously to BMS must be sent to

BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in the Investigator's Brochures and/or Package Inserts.

8.1 IND Agents

8.1.1 Description

Product information table: please also see respective product investigator brochures

Table	**Product Description**				
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab BMS-936558-01 Solution for Injection*	100 mg (10 mg/mL)	10 mL vial	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

*Nivolumab may be labeled as bms-936558-01 solution for injection

8.1.2 **Storage and Stability**

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

For additional details on prepared drug storage and use time of nivolumab or ipilimumab under room temperature/light and refrigeration, please refer to the bms-936558 (nivolumab) and ipilimumab investigator brochure section for "recommended storage and use conditions" and in Appendix C.

8.1.3 **Handling**

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

8.1.4 **Availability**

Free of cost, investigational supply of nivolumab and ipilimumab will be provided by Bristol-Myers Squibb.

8.1.5 **Ordering**

Dana-Farber Research Pharmacy will request supply of nivolumab and ipilimumab from Bristol-Myers Squibb by submitting the order form.

8.1.6 **Accountability**

Accountability for investigational agents at the study site is the responsibility of the sponsor-investigator. Study drug will be dispensed only to eligible patients by Dana-Farber Research Pharmacy. The appropriate study personnel will maintain records of study drug receipt and dispensing at Dana-Farber Research Pharmacy. A careful record of the inventory and disposition of the agent will be maintained, using the NCI Drug Accountability Record Form (DARF).

8.1.7 **Destruction and Return**

Unused supplies and expired supplies of the investigational agents will be destroyed on site, by the Dana-Farber Research Pharmacy.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

Patients will be asked to provide mandatory blood samples at several time points as specified in the study calendar. Strongly recommended sequential biopsies, if safely accessible, at specified

time points will provide fresh tumor samples for analysis.

Correlative blood samples will be drawn prior to treatment, at 2 weeks after start with either nivolumab or ipilimumab (end of week 2, prior to week 3) at week 9, and at 6 and 12 months after start of protocol treatment, and at the time of treatment discontinuation (or within 30 days after). Cell-free DNA will be analyzed using NexGen sequencing to detect the presence and changes in the amount of cell free DNA (cfDNA). Flow-based cell sorting will be used to determine if circulating tumor cells are present and how the proportion of CD4, CD8, and Treg cells changes over the course of treatment. These changes will be correlated with clinical response. We will also profile T cell neoantigens.

Blood collection tubes as specified below will be obtained at the time points indicated in the study table. There is a +/- 3 day window (for obtaining these samples except for collection at W2 prior to start of second drug). These collections will be taken at the time of routine blood collection time points required for this study. Specimens will be processed on site according to instructions below and shipped (via traceable carrier) to Dana-Farber Cancer Institute. Once the shipment is received, samples will be subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute.

All tubes should be transported at (ambient) room temperature. Collection kits containing the appropriate tubes will be sent to participating sites.

Sequential biopsies are strongly recommended for patients with accessible tumor. These will consist of core needle biopsies and if necessary open biopsies.

Samples will be subject to immune cell analysis by flow cytometry as previously described. Live cells will be used for in vitro analysis of immune response in the organotypic tumor spheroid culture system in either the lab of Dr. David Barbie or the Bowden lab where response to nivolumab and ipilimumab will be determined. The responses seen in vitro will be correlated with clinical response. Biopsies may be obtained prior to treatment start, after 2 weeks of treatment with one drug alone, following restaging CT scans at 8 weeks (within a 10 day window) and at time of progression.

TIL's will undergo RNA sequencing to determine changes of expression in response to nivolumab, ipilimumab or both drugs combined. This will allow to identify antigens involved in immune response as well as resistance mechanisms that could account for primary or secondary resistance and tumor progression.

The tissue will be used to assess PD-1, PDL-1 expression, T-cell infiltration on IHC and flow cytometry.

Whole exome sequencing (WES) and RNA sequencing to assess changes in expression profile will be performed. Single cell sequencing of infiltrating immune cells will be performed as well.

Tissue will be stained for STING protein expression.

These studies will provide information that will help to identify patterns indicative of response and resistance to immunotherapy with nivolumab and ipilimumab in thyroid cancer.

As additional hypotheses about the drivers of response and resistance arise over the course of the study, investigators may choose to use additional tissue testing methodologies beyond those laid out above. Investigators may also request additional archival tissue for such testing.

Non-DF/HCC sites will be responsible for shipping samples via overnight delivery to DF/HCC on the day of collection. DF/HCC will provide shipment instructions to participating sites. This applies only to biomarker samples (routine laboratory samples will be analyzed locally).

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 3 weeks prior to study registration. If these screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline cycle 1 day 1 values and do not need to be repeated. Each treatment cycle will be 6 weeks long. Scans must be done $\leq$4 weeks prior to study registration.

As detailed in the Study Calendar, a negative pregnancy test in women of child-bearing potential must be documented within 24 hours of the first dose of study drug.

Laboratory evaluations do not need to be repeated to meet eligibility criteria on date of first treatment dose, if they were done within 3 days of the first treatment dose.

In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next treatment dose.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

	Screening	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11 and Beyond[h]	End of Treatment[h]	Follow up visit 30 (+/-7) days after the last dose
Informed consent	X								
Medical History	X								
ECG	X							X[j]	
B-HCG (WOCBP only) [a]	X	X			X			X	

Physical exam (Ht, Wt, VS, PS) [b]	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X
Routine labs [c]	X	X	X	X	X	X	X	X	X
Tumor Markers [d]	X				X				
Adverse event evaluation		X							
Radiologic evaluation [e]	X	X							
Correlative blood collection	X[i]		X[i]			X[i]	X[i]		
Correlative tissue collection	X [f]		X [g]			X [g]			
Nivolumab		Every 2 weeks for a maximum of 24 months (starting on week 1 in arms 1 and 3 and in week 3 in arm 2)							
Ipilimumab		Every 6 weeks for a maximum of 24 months (starting on week 3 in arm 1 and week 1 in arms 2 and 3)							

a) Serum or urine at screening and at day 1 of each cycle
b) Physical exam is symptom directed. Height measured at screening only
c) Routine labs include: CBC w/differential, Chemistry panel including: Albumin, LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, lipase, TSH, Free T4. TSH and Free T4 are only required at screening and then at day 1 of each cycle starting with cycle 2.
d) At each cycle, collect Serum calcitonin, CEA (carcinoembryonic antigen), and CA19-9 for MTC, and Thyroglobulin antibodies (TgAb), and thyroglobulin (Tg) for DTC.
e) Scans every 8 weeks during protocol therapy, or as clinically indicated
f) Fresh biopsy or archival tissue
g) Fresh biopsy is strongly recommended (if safe to perform), at weeks 3 and 9 and at treatment discontinuation
h) Participants will be followed for response until treatment discontinuation or disease progression (whichever comes last) and for survival for 2 years from study registration. Post end of protocol treatment, if first disease progression has not been confirmed, tumor assessments are to continue every 3 months (+/- 1 month) until first disease progression, death, or 2 years post study registration. After first disease progression has been confirmed, patients will be followed for survival by phone only, every 3 months (+/- 1 month) until death or 2 years post study registration, whichever occurs first
i) Correlative blood samples will be collected at screening (any time after consent and before week 1 treatment) then during treatment at week 3, week 9; after 6 and 12 months of start of treatment; and following treatment discontinuation (EOT sample can be collected on the day of EOT visit or within 30 days afterwards)
j) EOT ECG can occur on the day of EOT visit or within 30 days afterwards

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks (or as clinically indicated). In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

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

11.1.1 Definitions

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

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

11.1.2 Disease Parameters

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

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

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable)

since they are, by definition, simple cysts.

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of Disease

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

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

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

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

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

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

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

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

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

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST

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

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

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

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.
Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

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

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

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

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

initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of New Lesions

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

11.1.4.4 Evaluation of Best Overall Response

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-	No	SD	Documented at least once ≥4

	PD/not evaluated			wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

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

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the participants' files and radiological images is the best approach.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Instructions for AE reporting can be found in Section 7.

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Study team is responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

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

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

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

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

13. STATISTICAL CONSIDERATIONS

Prior to Amendment 7, patients with DTC, MTC, and ATC were randomized to Arms 1 and 2. With approval of Amendment 7, patients with ATC were no longer randomized into Arms 1 and 2, but rather registered into Arm 3 (for a total of n=7 patients with ATC entered into Arms 1, 2, and 3). With approval of Amendment 12, the accrual for the ATC cohort was increased to n=10.

The primary objective of this trial is to evaluate efficacy in terms of best overall response rate (CR+PR) for patients with DTC. The purpose of the randomization with nivolumab and ipilimumab starting sequentially is to provide opportunities via the correlatives to study the specific immunologic changes that occur in response to either drug alone as well as both drugs in combination. Although patients will be randomized between arms, no differences in terms of efficacy are expected, therefore, for the primary endpoint of response, the arms will be analyzed together.

A two -stage design (Simon's minimax design) will be used to minimize the number of pts enrolled. Twenty-three eligible patients with differentiated thyroid cancer (DTC) who start protocol treatment are to be accrued in the first stage. If there are ≤ 2 patients with DTC with

disease in response, accrual to this trial will be closed with the expectation that there is little evidence that the response rate will reach 25%. The probability that the trial will close early is 59% if the true response rate is 10%. If there are >2 patients with DTC with disease in response, accrual will continue until a total of 32 eligible patients with DTC who start protocol treatment are entered. If there are >5 patients with DTC with disease in response among 32 eligible patients with DTC who began protocol treatment, further testing of this regimen will be considered. If the true response rate is 25%, the probability of concluding the regimen is effective is 84%, if the true response rate is 10%, the probability of concluding the regimen is effective is 9%. In addition, n=7 medullary and n=10 anaplastic thyroid patients will also be included as exploratory cohorts. Allowing for patients to be declared ineligible and/or not start protocol treatment after registration, a total of 54 pts will be entered into Arms 1, 2, and 3. The following stratification factor will be used for Arms 1 and 2 only in order to prevent imbalance across treatment arms:

- Histology (differentiated thyroid cancer vs. medullary thyroid cancer)

(Prior to Amendment 7, patients with anaplastic thyroid cancer were also randomized, and as of approval of Amendment 7, patients with anaplastic thyroid cancer will no longer be randomized, they will instead be entered into Arm 3 (see schema and section 5 for details)).

The primary efficacy population includes all eligible patients with DTC who begin protocol treatment. Best overall response will be summarized as a proportion with a corresponding exact 95% confidence interval (CI) (if the trial closes to accrual after the first stage), or a corresponding 95% two-stage CI if the trial closes to accrual after the second stage. Best overall response for patients with medullary and anaplastic thyroid cancer will also be summarized.

For secondary objectives: Adverse events will be classified and graded according to the CTCAE v.4.0. Frequencies of adverse events will be summarized among patients who begin protocol therapy overall and within histologic type. The distributions of progression and survival will be estimated within histologic subtype using a Kaplan-Meier method with corresponding 95% confidence intervals for the median or time-specific event time. Several correlative studies are also planned. Given the small sample size of this trial, these studies are exploratory. Samples will be collected at baseline and at post-baseline timepoints as outlined in the protocol. Markers from the patients with evaluable samples will be summarized descriptively and graphically. Within subject changes in markers will also be analyzed. Assuming 32 patients with DTC with baseline and a post-baseline value provides 82% power to detect .54 SD mean difference (Wilcoxon sign rank test two-sided 0.05 alpha level). Markers from the patients with evaluable samples within medullary and anaplastic thyroid cancer will also be summarized descriptively.

With an estimated monthly accrual of 1-2 patients, the first stage of accrual for patients with DTC is estimated to complete accrual in approximately 18 months. Due to possible delays in initiation of approval at other sites, in initiation of accrual itself, accrual to the first stage could take 24 months. As is customary with this type of design, accrual will be suspended after the first stage (n=23 eligible patients) in order to assess outcome; however, this suspension is also dependent on the actual observed accrual rate and the number of patients with confirmation of disease response status while the first stage of the trial is accruing

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

15. REFERENCES

1. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892-9.
2. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319-28.
3. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. The New England journal of medicine. 2015;372(7):621-30.
4. Brose M, Schlumberger M, Tahara M, Wirth LJ, Robinson B, Elisei R, et al. Effect of age on the efficacy and safety of lenvatinib for the treatment of 131i-refractory differentiated thyroid cancer in the phase 3 select study. Journal of Geriatric Oncology.5:S22-S3.
5. Mehnert J, Varga A, Brose M, Aggarawal A, Lin C, Prawira A, et al. Pembrolizumab for advanced papillary or follicular thyroid cancer: preliminary results from the phase 1b KEYNOTE-028 study. ASCO annual Meeting 2016, Abstract # 6091.
6. Besic N, Hocevar M, Zgajnar J, Pogacnik A, Grazio-Frkovic S, Auersperg M. Prognostic factors in anaplastic carcinoma of the thyroid-a multivariate survival analysis of 188 patients. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie. 2005;390(3):203-8.
7. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. The Journal of experimental medicine. 2000;192(7):1027-34.
8. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nature immunology. 2001;2(3):261-8.
9. Carter L, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. European journal of immunology. 2002;32(3):634-43.
10. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS letters. 2004;574(1-3):37-41.

11. Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends in immunology. 2001;22(5):265-8.
12. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity. 1999;11(2):141-51.
13. Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291(5502):319-22.
14. Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang J, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. Nature medicine. 2003;9(12):1477-83.
15. Salama AD, Chitnis T, Imitola J, Ansari MJ, Akiba H, Tushima F, et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. The Journal of experimental medicine. 2003;198(1):71-8.
16. Blazar BR, Carreno BM, Panoskaltsis-Mortari A, Carter L, Iwai Y, Yagita H, et al. Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-gamma-dependent mechanism. Journal of immunology. 2003;171(3):1272-7.
17. Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. International immunology. 2005;17(2):133-44.
18. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proceedings of the National Academy of Sciences of the United States of America. 2002;99(19):12293-7.
19. Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer research. 2003;63(19):6501-5.
20. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature medicine. 2002;8(8):793-800.
21. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer research. 2005;65(3):1089-96.
22. Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer research. 2004;64(3):1140-5.
23. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clinical cancer research : an official journal of the American Association for Cancer Research. 2004;10(15):5094-100.
24. Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2005;11(8):2947-53.
25. Tsushima F, Tanaka K, Otsuki N, Youngnak P, Iwai H, Omura K, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol. 2006;42(3):268-74.

26. Thompson RH, Webster WS, Cheville JC, Lohse CM, Dong H, Leibovich BC, et al. B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in patients with renal cell carcinoma. Urology. 2005;66(5 Suppl):10-4.
27. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005;104(10):2084-91.
28. Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. J Mol Med (Berl). 2003;81(5):281-7.
29. Azuma T, Yao S, Zhu G, Flies AS, Flies SJ, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood. 2008;111(7):3635-43.
30. Hino R, Kabashima K, Kato Y, Yagi H, Nakamura M, Honjo T, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer. 2010;116(7):1757-66.
31. Velu V, Titanji K, Zhu B, Husain S, Pladevega A, Lai L, et al. Enhancing SIV-specific immunity in vivo by PD-1 blockade. Nature. 2009;458(7235):206-10.
32. Wang C, Thudium KB, Han M, Wang XT, Huang H, Feingersh D, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer immunology research. 2014;2(9):846-56.
33. Habicht A, Dada S, Jurewicz M, Fife BT, Yagita H, Azuma M, et al. A link between PDL1 and T regulatory cells in fetomaternal tolerance. Journal of immunology. 2007;179(8):5211-9.
34. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(9):4275-80.
35. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. The New England journal of medicine. 2013;369(2):122-33.
36. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine. 2015;373(1):23-34.
37. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. The New England journal of medicine. 2010;363(8):711-23.
38. Lorch J, Busaidy N, Ruan D. A phase II study of everolimus in patients with aggressive RAI refractory (RAIR) thyroid cancer. ASCO 2013.
39. Wagle N, Grabiner BC, Van Allen EM, Amin-Mansour A, Taylor-Weiner A, Rosenberg M, et al. Response and acquired resistance to everolimus in anaplastic thyroid cancer. N Engl J Med. 2014;371(15):1426-33.
40. Angell TE, Lechner MG, Jang JK, Correa AJ, LoPresti JS, Epstein AL. BRAF(V600E) in Papillary Thyroid Carcinoma Is Associated with Increased Programmed Death Ligand 1 Expression and Suppressive Immune Cell Infiltration. Thyroid. 2014;24(9):1385-93.
41. Pedicord VA, Cross JR, Montalvo-Ortiz W, Miller ML, Allison JP. Friends Not Foes: CTLA-4 Blockade and mTOR Inhibition Cooperate during CD8+ T Cell Priming To Promote Memory Formation and Metabolic Readiness. The Journal of Immunology. 2015;194(5):2089-98.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX D METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective OR one less effective method of contraception as listed below:

Highly Effective Methods of Contraception

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure

- Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence

- Complete abstinence is defined as the complete avoidance of heterosexual intercourse.
- Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- Subjects who choose complete abstinence must continue to have pregnancy tests
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
- The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Less Effective Methods of Contraception

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide
4. Male or female condom with or without spermicide*
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

* A male and a female condom must not be used together.

Unacceptable Methods of Contraception

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)

3. Spermicide only
4. Lactation amenorrhea method (LAM)