Academic and Community Cancer Research United (ACCRU)

Combination Targeted Therapy with Pembrolizumab and Lenvatinib in Progressive, Radioiodine-Refractory Differentiated Thyroid Cancers: A Phase II Study

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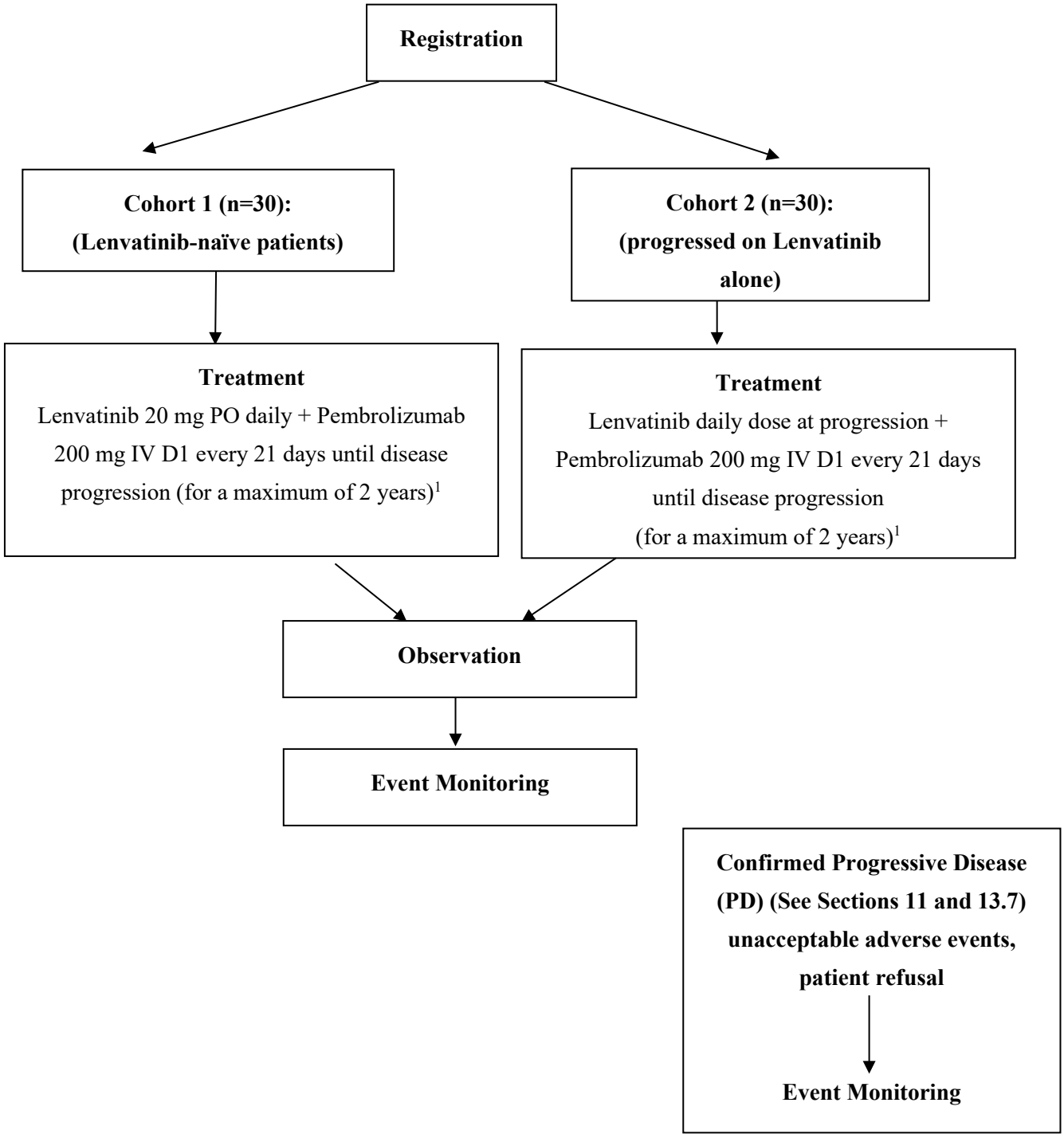

[1] Cycle length= 21 days

Generic name: Pembrolizumab Brand name(s): Keytruda Availability: Merck	Generic name: Lenvatinib Brand name(s): Lenvima Availability: Eisai

1.0 Background

1.1 Thyroid Cancer – Incidence and Standard of Care

More than 500,000 people in the United States have a diagnosis of thyroid cancer, and the incidence is steadily growing, with an estimated 62,000 new cases in 2014. Thyroid cancer is the 5th most commonly diagnosed cancer in women. Although localized differentiated thyroid cancer (DTC) is generally managed by surgery and radioactive iodine therapy, approximately 10% of patients develop progressive invasive primary disease and 5% develop distant metastases (Howlader N, et. al., 2010)[1]. Many of these patients develop radioiodine-refractory disease, and their prognosis is only minimally improved with tyrosine kinase inhibitors (TKIs). Treatment with sorafenib does provide some benefit, with an overall partial response (PR) rate of 12% and a 5-month increase in progression-free survival (PFS). However, no complete response (CR) is observed and the partial responses are not durable (Brose MS, et. al., 2014)[2]. Lenvatinib, which is now approved as standard of care for progressive DTC, achieved a 1.5% CR and a 63.2 % PR and extended PFS by 14.7 months (Schlumberger M, et. al., 2015)[3]. While these data are encouraging, TKI monotherapies are not curative.

1.2 Rationale for Immune-based Therapies in Aggressive DTC

The thyroid is one of the most immunogenic organs in the body. The prevalence of autoimmune thyroiditis in the general population is approximately 5-10%, and nearly 30% of patients with DTC have thyroid autoantibodies. Furthermore, checkpoint blockade therapies (i.e., anti-CTLA-4 and anti-PD-1) commonly lead to thyroiditis. As in other inflammation-associated cancers, thyroiditis may contribute to tumorigenesis, tumor elimination, and, at later stages, tumor progression. It is likely that a subset of the autoimmune T cell response is capable of recognizing the thyroid tumor in many patients with DTC.

A growing body of literature has described the tumor-associated immune response in thyroid cancers (French JD, 2013)[4]. Similar to other types of cancer, the immune milieu in thyroid cancer includes immature dendritic cells, M2-polarized macrophages, and suppressive or dysfunctional T cells. Despite these classic signs of immune dysregulation, most patients with thyroid cancer have relatively indolent disease. Patients with invasive primary disease progress slowly compared to other types of inoperable cancers, with an average survival rate of 70% at 5 years. Lymph node (LN) metastasis, while common in patients with DTC, rarely lead to distant metastasis and can persist for years without evident progression. Given the potential immunogenicity and relatively indolent nature of DTC, we hypothesize that DTC may be exceptionally sensitive to immune-targeted therapies.

1.3 Tregs and T Cell Exhaustion in DTC

Our previous (French JD, Kotnis GR, et. al., 2012 and French JD, Weber ZJ, et. al., 2010)[5, 6] and ongoing studies suggest that T cell dysfunction plays a role in DTC progression. Specifically, $FoxP3^+$ regulatory $CD4^+$ T cells (Tregs) were found at increased frequencies in both primary tumors (T1-T4) and tumor-involved lymph nodes (TILN) compared to blood and uninvolved lymph nodes (UILN), respectively. Treg frequency in primary tumors correlated with lymph node metastasis, and increased levels of Tregs were found in TILN from patients with recurrent disease. Programmed-death-1

(PD-1)$^+$ T cells were also enriched in primary tumors (T1-T4) and TILN. Although we have not yet shown disease significance in primary tumors, high frequencies of PD-1$^+$ T cells in TILN were associated with extranodal invasion, a sign of more aggressive disease. Ongoing studies using archived tissues from patients with inoperable, invasive T4 tumors and distant metastases revealed intratumoral CD8$^+$ T cells and FoxP3$^+$ Tregs in 14 of 15 primary T4 tumors and 1 of 4 metastases tested to date. PD-1$^+$ T cells were present in peritumoral and more distal regions in a subset of patients (n=6). PD-L1 was expressed by the primary tumor and infiltrating leukocytes in 8 (53%) of 15 samples tested, respectively. Furthermore, preliminary studies in progressive DTC suggest that Tregs (9-14%) and PD-1$^+$CD8$^+$ (27-46%) T cell frequencies are elevated in peripheral blood in a subset of patients.

To further investigate the phenotype and functional capacity of PD-1$^+$ T cells in DTC, we isolated tumor-associated lymphocytes from grossly-involved lymph nodes (Severson JJ, et. al., 2015)[7]. PD-1$^+$CD8$^+$ T cells were enriched (5-38% of CD8$^+$) in 7 of 11 of TILNs and displayed an exhausted molecular phenotype (i.e., CD69^{hi}, CD127$^{+/-}$, CD27^{hi}). T cell immunoglobulin and mucin domain protein 3 (Tim-3) was co-expressed with PD-1. *Ex vivo* functional studies of CD8$^+$ T cells revealed that stimulated cytokine (IL-2, TNFα, and IFNγ) production was diminished to varying degrees. However, *ex vivo* proliferative potential remained largely intact. Thus, PD-1 expression is a sign of T cell dysfunction in patients with persistent lymph node involvement. However, exhaustion may be in the early stages and readily reversible. Analysis of PD-L1 expression on fresh tumor samples from TILN revealed that the majority of tumors (8/11) express PD-L1 and may contribute directly to PD-1-mediated T cell dysfunction. In line with our previous studies, Tregs were elevated (13-39% of CD4$^+$) in TILN from all 11 patients, regardless of PD-1 phenotype. We predict that Tregs may contribute to the development of T cell exhaustion; and, even in the absence of exhaustion, may pose a substantial barrier to the success of immune-targeted and tumor-targeted therapies.

1.4 Antiangiogenic Therapy

Angiogenesis, the formation of new blood vessels from a preexisting vascular network, is essential for tumor growth and metastasis. Many molecules have been implicated as positive regulators of angiogenesis, including VEGF, acidic fibroblast growth factor (aFGF), basic FGF (bFGF), hepatocyte growth factor (HGF), interleukin (IL)-8, and platelet-derived growth factor (PDGF). (Kobayashi M, et. al., 2013)[19] In adults, physiological angiogenesis occurs during the female reproductive cycle and in wound healing. In addition to tumor growth, abnormally enhanced neovascularization is also observed in rheumatoid arthritis, psoriasis, and diabetic retinopathy. Of the numerous molecules that have been shown to have angiogenic properties, VEGF has been identified as a crucial regulator of both physiologic and pathologic angiogenesis with increased expression being associated with a poor prognosis in many human tumor types. (Rizvi NA, et. al., 2015, Taube JM, et. al., 2014, Tumeh PC, et. al., 2014, Qing W, et. al., 2012) [21-24] VEGF acts primarily on endothelial cells to promote their proliferation and three-dimensional organization for tube formation and is thought to be the most potent and specific proangiogenic factor. VEGF exerts its effects through two cell membrane bound receptors, Flt-1 and KDR, of which KDR is thought to be more important. There is increasing evidence that KDR is the major mediator of endothelial cell proliferation and survival as well as tube formation and microvascular permeability. KDR undergoes dimerization and ligand-dependent tyrosine phosphorylation, producing a mitogenic,

chemotactic and prosurvival signal. Consequently, a KDR TK inhibitor would be expected to exert a potent inhibitory effect on tumor growth and metastasis formation.

1.5 Pembrolizumab Mechanism of Action

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (MK-3475, Keytruda™) is a potent and highly selective humanized

monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Clinical Experience with Pembrolizumab

Melanoma: Pembrolizumab has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma. Approval was based on the results of a multicenter, open-label, randomized trial, P001. 173 patients with unresectable or metastatic melanoma with disease progression on ipilimumab and, if BRAF V600 mutation positive, prior treatment with a BRAF inhibitor, were randomized to receive pembrolizumab 2 mg/kg (n=89) or 10 mg/kg (n=84) intravenously once every 3 weeks until disease progression or unacceptable toxicity.

Key exclusion criteria were an autoimmune disease, a medical condition that required immunosuppression, and/or a history of severe immune-mediated adverse reactions from treatment with ipilimumab. Severe immune-mediated adverse reactions were defined as any CTCAE Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks.

The ORR was 24% (95% CI: 15, 34) in the 2 mg/kg arm, consisting of one complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had disease progression at 2.8, 2.9, and 8.2 months after initial response. The remaining 18 patients (86%) have ongoing responses, ranging from 1.4+ to 8.5+ months; 8 patients have ongoing responses of 6 months or longer. Similar ORR results were observed in the 10 mg/kg arm.

The most common (greater than or equal to 20%) adverse reactions among patients receiving pembrolizumab 2 mg/kg every 3 weeks were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

The most frequent (greater than or equal to 2%) serious adverse drug reactions observed with pembrolizumab were renal failure, dyspnea, pneumonia, and cellulitis. Additional clinically significant immune-mediated adverse reactions included pneumonitis, colitis, hypophysitis, hyperthyroidism, hypothyroidism, nephritis, and hepatitis.

Pembrolizumab is now being studied extensively in multiple cancer types, and in combination multiple antineoplastic agents.

Lung Cancer: The safety of pembrolizumab was studied in 550 patients with advanced NSCLC. The most common side effects of pembrolizumab included fatigue, decreased appetite, shortness of breath or impaired breathing (dyspnea) and cough. Pembrolizumab also has the potential to cause severe side effects that result from the immune system effect of pembrolizumab (known as “immune-mediated side effects”).

The effectiveness of pembrolizumab for this use was demonstrated in a subgroup of 61 patients enrolled within a larger multicenter, open-label, multi-part study. The subgroup consisted of patients with advanced NSCLC that progressed following platinum-based chemotherapy or, if appropriate, targeted therapy for certain genetic mutations (ALK or EGFR). This subgroup also had PD-L1 positive tumors based on the results of the 22C3 pharmDx diagnostic test. Study participants received 10 mg/kg of pembrolizumab every

two or three weeks. The major outcome measure was overall response rate (percentage of patients who experienced complete and partial shrinkage of their tumors). Tumors shrank in 41 percent of patients treated with pembrolizumab and the effect lasted between 2.1 and 9.1 months.

In the 550 study participants with advanced NSCLC, severe immune-mediated side effects occurred involving the lungs, colon and hormone-producing glands. Other uncommon immune-mediated side effects were rash and inflammation of blood vessels (vasculitis). Women who are pregnant or breastfeeding should not take pembrolizumab because it may cause harm to a developing fetus or newborn baby. Across clinical studies, a disorder in which the body's immune system attacks part of the peripheral nervous system (Guillain-Barre Syndrome) also occurred.

The FDA granted pembrolizumab breakthrough therapy designation for this indication because Merck demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over available therapies. The drug also received priority review status, which is granted to drugs that, at the time the application was submitted, have the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition.

Thyroid Cancer: There is an ongoing basket trial (KEYNOTE-028 (NCT02054806)) which has enrolled patients with advanced thyroid cancer to a single agent pembrolizumab (200 mg iv every 3 weeks) study. Preliminary data from the thyroid cohort in this trial was presented at the 2016 American Society for Clinical Oncology (Mehnert JM, et al, J Clin Oncol 34, 2016 (suppl; abstr 6091)). The study enrolled 22 patients with DTC, with a median duration of follow-up of 74 weeks (29-87 weeks). No patients achieved a CR (0%) and 2 patients had a PR (9.1%), with 12 achieved SD (54%).

1.6 Lenvatinib Mechanism of Action

VEGF is a crucial regulator of both physiologic and pathologic angiogenesis. Its increased expression is associated with a poor prognosis in many cancers. VEGF exerts its effects through two cell membrane receptors, fms-like tyrosine kinase 1/vascular endothelial growth factor receptor 1 (Flt-1/VEGFR-1) and kinase insert domain receptor (KDR/VEGFR-2). (Kobayashi M, et. al, 2013)[19] Lenvatinib is an orally available potent inhibitor of the split-kinase family of transmembrane growth factor receptors including Flt-1/VEGFR-1 and KDR/VEGFR-2. Receptor tyrosine kinase cell free assays demonstrate IC50 values of 22 (Flt-1/VEGFR-1) and 4 nM (KDR/VEGFR-2). Additionally, lenvatinib potently inhibits vascular endothelial growth factor receptor 3 (VEGFR-3, IC50 5nM), fibroblast growth factor receptor (FGFR)-1 (IC50 46 nM),2,3,4 and platelet-derived growth factor receptor (PDGFR, IC50 39 nM) beta tyrosine kinases. Lenvatinib also inhibits (IC50 5.2 nM) SCF-driven tube formation of HUVEC, which express SCF receptor, KIT.

<u>Clinical Experience with Lenvatinib</u>

A global Phase 1 program in patients with solid tumors has been conducted with lenvatinib to determine the safety, tolerability and pharmacokinetics of three different regimens including continuous once daily dosing. Pharmacokinetic analysis has

demonstrated that lenvatinib is rapidly absorbed with maximum concentrations observed from 1 to 3 hours post dose. Lenvatinib elimination occurs with a biexponential decline composed of an initial rapid decline followed by a slower decline. The terminal half-life is approximately 30 hours and steady state is achieved within 5 days. A dose dependent increase in soluble VEGF, consistent with an anti-angiogenic effect was observed during 2 weeks of continuous dosing.

Hypertension and proteinuria were the most common dose limiting toxicities (DLT). A dose of 25 mg once daily was found to be the maximum tolerated dose (MTD) for the once daily continuous dosing schedule. A cohort of 24 patients treated at this dose level established the safety and tolerability of the lenvatinib 25 mg dose for once daily continuous dosing. To simplify drug administration, a dose of 24 mg (two 10 mg capsules + one 4 mg capsule) once daily was selected for ongoing lenvatinib development.

Lenvatinib - Clinical Experience in Thyroid Cancer

Phase II study of lenvatinib in radioiodine-refractory DTC led to the SELECT trial, a global, placebo-controlled randomized phase III trial of lenvatinib in radioiodine-refractory progressive DTC. The primary endpoint was PFS, which was significantly prolonged with lenvatinib versus placebo (median 18.3 months versus 3.6 months, respectively; hazard ratio [HR] 0.21; 99% confidence interval 0.14–0.31, $P<0.001$). Lenvatinib PFS benefit was observed in all predefined subgroups, including patients who received 0 (n=299) or 1 (n=93) prior tyrosine-kinase inhibitor therapies (HR: 0.20 and 0.22, respectively). Lenvatinib significantly improved ORR versus placebo (64.8% [4 complete; 165 partial responses] versus 1.5%; $P<0.001$). Median overall survival has not been reached. For lenvatinib, treatment-related adverse effects (>40%, all grades) were hypertension (67.8%), diarrhea (59.4%), fatigue/asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%); adverse effects were managed with dose reductions and standard interventions. Discontinuations due to adverse effects occurred in 37 (14.2%) lenvatinib-treated and 3 (2.3%) placebo-treated patients. In the lenvatinib arm, 6/20 treatment-emergent deaths were considered drug-related.

1.7 Rationale for Combination Therapy with Pembrolizumab (MK-3475) and Lenvatinib

We predict that successful elimination of aggressive DTC will require both cessation of tumor growth and activation of the anti-tumor immune response.

Based on preliminary data, we predict that release of the PD-1 checkpoint and simulanteous elimination of Treg suppressive activity will be essential for immune activation in patients with advanced DTC. Disruption of PD-1/PD-L1 interactions with MK-3475 (Pembrolizumab) would release a major checkpoint blockade in patients with PD-1+ tumor-specific T cells, encouraging immune-mediated tumor destruction. Importantly, Tregs have been shown to express both PD-1 and PD-L1, and blockade of PD-1/PD-L1 interactions is thought to inhibit the induction, maintenance, and function of Tregs. (Amarnath S, et. al, 2011, Duraiswamy J, et. al., 2013, Francisco LM, et. al., 2009, Kitazawa Y, et. al., 2007)[8-11] Thus, pembrolizumab may also inhibit the suppressive effects of tumor-associated Tregs.

A number of studies have investigated the effects of multi-target tyrosine kinase inhibitors on the immune system. Sorafenib was initially developed to target RAF, but it also inhibits VEGFR-2, VEGFR-3, PDGFR-β, c-kit and FLT3 (Adnane L, et. al., 2006,

and Ahmad T, et. al., 2004)12, 13. Of note, Tregs are known to express VEGFR-214. Inhibition of VEGF activity by anti-VEGFR-2 antibody treatment inhibits Treg proliferation (Terme M, et. al., 2013)14. Sorafenib inhibited Treg suppression in vitro (Busse A, et. al., 2011 and Cabrera R, et. al., 2013)15, 16 and reduced the number of peripheral Tregs in cancer patients in 2 of 3 independent studies (Chen ML, et. al., 2014, Florcken A, et. al., 2012 and Kobayashi M, et. al., 2013)17-19. We believe that lenvatinib may have a more potent effect on Treg function in patients with advanced thyroid cancer based on its more potent effects on VEGFR-2.

We hypothesize that combination pembrolizumab and lenvatinib therapy will generate significantly improved CR compared to pembrolizumab alone (MK3475-028/KEYNOTE-28, ongoing basket trial that includes DTC, that demonstrated a CR of 0%) or the historical CR of lenvatinib alone (1.5%).

1.8 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, was the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

The starting dose of lenvatinib 24 mg by mouth daily is the FDA-approved dose for radioiodine-refractory progressive differentiated thyroid carcinoma based upon the dosing used in the phase III SELECT trial that established the efficacy of lenvatinib in this setting. An ongoing phase Ib basket trial of lenvatinib plus pembrolizumab in solid tumors (thyroid was not included), showed good tolerability of the combination and recommends a starting dose of 20 mg daily lenvatinib in combination with 200 mg iv pembrolizumab every 3 weeks, which will be the staring doses in Cohort 1 (personal communication). Patients entering Cohort 2 will have progressed on lenvatinib. These patients will remain on the dose they are taking at the time of study entry, which may have been previously reduced for side effect management, and will not exceed 20 mg by mouth daily.

1.9 Rationale for Correlative Research

1.91 Recent successes of anti-PD-1/PD-L1 checkpoint inhibitors (e.g., pembrolizumab, and nivolumab) have reinvigorated the field of cancer immunotherapy (Hamid O, et. al., 2013 and Rizvi NA, et. al., 2015)[20, 21]. Response rates have ranged from 13% to 37% in patients with progressive cancers that have failed multiple lines of therapy. Post-trial analyses have attempted to define molecular markers that correlate with tumor regression. Response to nivolumab was associated most strongly with expression of PD-L1 by the tumor and did not significantly correlate with infiltrating lymphocytes. PD-1 was expressed by tumor-infiltrating lymphocytes in 7/10 of responders and 9/18 non-responders and did not significantly correlate with a clinical response (Taube JM et. al., 2014)[22]. In contrast, response to pembrolizumab was strongly associated with a high frequency of $CD8^+$ or $PD\text{-}1^+$ T cells, either at the invasive margin or infiltrating the tumor, and, to a lesser degree, expression of PD-L1 (Tumeh PC, et. al., 2014)[23]. In the proposed correlative research studies, we will assess $CD8^+$ and $PD\text{-}1^+$ T cell frequency and expression of PD-L1 and PD-L2 by tumor and associated leukocytes in primary tumor samples and pre-treatment

biopsies by immunohistochemistry. We will also assess PD-1 expression and its functional consequences in peripheral blood leukocytes before and throughout treatment using flow cytometry.

1.92 Tregs have been shown to express both PD-1 and PD-L1, and blockade of PD-1/PD-L1 interactions is thought to inhibit the induction, maintenance, and function of Tregs (Duraiswamy J, et. al., 2013)[9, 11]. A number of studies have investigated the effects of multi-target tyrosine kinase inhibitors on the immune system. Inhibition of VEGF activity by anti-VEGFR-2 antibody treatment inhibits Treg proliferation (Terme M, et. al., 2013)[14]. Sorafenib, a multikinase inhibitor that targets VEGFR-2, has been shown to inhibit Treg suppression *in vitro* and reduce the number of peripheral Tregs in cancer patients (Busse A, et. al., 2011 and Cabrera R, et. al., 2013)[15, 16]. Thus, both pembrolizumab and lenvatinib may inhibit the suppressive effects of tumor-associated Tregs. We plan to investigate whether the frequency of $FoxP3^+$ Tregs in the primary tumor and pre-treatment biopsy, as determined by immunohistochemistry for FoxP3, correlates with response to treatment. We will also investigate the frequency and phenotype of Tregs in peripheral blood before and throughout treatment using flow cytometry.

1.93 Tumor associated macrophages (TAM) and immature dendritic cells (iDC) have been described in primary thyroid tumors. Increased frequencies of TAM were associated with lymph node metastasis in patients with DTC (Qing W, et. al., 2012)[24]. TAM in DTC expressed CD163 and IL-10 and have been proposed to play a role in tumor progression (Qing W, et. al., 2012)[24]. $CD1a^+$ iDCs were also found at high frequencies in DTC samples (Batistatou A, et. al, 2002, Ugolini C, et. al. 2007, and Scarpino S, et. al., 2000)[25-27]. We identified $PD\text{-}L1^+$ TAM in 12/15 pT4 DTC and PDTC samples. Pro-angiogenic VEGFA is well documented in its ability to inhibit DC maturation and support the generation of TAM and myeloid derived suppressor cells (MDSC) (Alfaro C, et. al., 2009, Almand B., et. al., 2000, Dikov MM, et. al., 2005, Gabrilovich D, et. al., 1998, Voron T, et. al., 2014)[28-32]. This immunosuppressive cellular network likely supports induction and maintenance of Tregs within the tumor microenvironment through production of IL-10 and TGFβ (Coffelt SB, et. al., 2011, Ghiringhelli F, et. al., 2005, and Huang B, et. al., 2006)[33-35]. We plan to investigate the frequency and phenotype of TAM and MDSC in tumor and blood samples, respectively.

1.94 Approximately 25% of patients with DTC produce thyroid-specific antibodies, most commonly against Tg and TPO (Fiore E, et. al., 2009 and Pacini F, et. al., 1988)[36, 37]. We predict that titers of these autoantibodies may be surrogate markers for the anti-tumor response with pembrolizumab and lenvatinib therapy.

1.95 Recent analyses of patients with melanoma that underwent treatment with anti-PD-1 (pembrolizumab, Merck) revealed a strong positive association between the number of mutations in the tumor and responsiveness to the checkpoint blockade therapy (Rizvi NA, et. al., 2015)[38]. While thyroid cancer, in general, is thought to be a have a low mutation burden, little is known about mutation frequency and antigenicity in more aggressive and metastatic cases. Here, we propose to investigate whether high frequency of mutations or type of mutation is associated with response to combination therapy.

1.96 It is likely that a subset of patients will not respond to treatment and will require alternative therapies. Numerous tumor-intrinsic and tumor-extrinsic factors will undoubtedly contribute to resistance (e.g., mutation load, MHCI expression, antigen presentation, immune suppressive factors). We plan to compare gene expression profiles by RNA-Seq from responders and non-responders using pre-treatment frozen and FFPE biopsy samples.

2.0 Goals

2.1 Primary

2.11 To investigate the clinical efficacy, as indicated by the rate of complete response (CR) per RECIST 1.1, of combination therapy with pembrolizumab and lenvatinib in lenvatinib-naïve patients with progressive radioiodine-refractory DTC (Cohort 1).

2.12 To determine the overall response rate (ORR) by the addition of pembrolizumab to patients with radioiodine-refractory DTC who have progressive disease on lenvatinib alone (Cohort 2).

2.2 Secondary

2.21 To determine the safety profile and toxicity of combination therapy with pembrolizumab and lenvatinib in patients with progressive DTC. (Cohort 1 and Cohort 2)

2.22 To determine progression-free survival (PFS) and overall survival (OS). (Cohort 1 and Cohort 2)

2.3 Correlative Research

2.31 To correlate tumor response (RECIST 1.1) with pretreatment frequency of CD8+ T cells in the primary and/or metastatic tumor. FFPE tumor samples will be evaluated for CD8+ T cells by immunohistochemistry. Staining intensity is scored on a 1^+ to 3^+ scale, and the percentage of positive cells per total lymphocytes is estimated (1 = <1%, 2 = 1-10%, 3 = 11-33%, 4 = 34-66%, 5 = 67-100%). Allred scores (intensity + percent positive) are generated for comparison between samples (Phillips T, et. al., 2007). Quantitation of the $CD8^+$ cells will be performed using the Aperio Scanscope AT2 system (20X, 0.5 μm/pixel resolution). Our collaborating pathologist will designate both peritumoral and intratumoral areas for differential quantitation using the Aperio ImageScope application, and annotated regions will be analyzed for positive staining using an Aperio colormetric thresholding algorithm. To extrapolate the number of positive cells per mm^2, 15 random cells will be chosen to determine the average pixels per positive CD8 event. The average number of CD8 pixels will be divided by the total positive pixels to determine the number of positive CD8 cells in the annotated regions. The number of CD8 cells divided by the area will estimate the number of positive cells per mm^2. (Cohort 1 and 2)

2.32 To correlate tumor response (RECIST 1.1) with pretreatment PD-L1 and PD-L2 levels in the primary and/or metastatic tumor. Tumors will be will be evaluated for PD-L1 (by QualTek Clinical Laboratories) and anti-PD-L2 (Biolegend MIH18) by immunohistochemistry, as described above. (Cohort 1 and 2)

2.33 To correlate tumor response (RECIST 1.1) with pretreatment frequency of lymphocytes expressing CD3, CD4, PD-1, FoxP3, or CD20, and of CD163+

macrophages. Cells types will be detected in pretreatment FFPE tumor tissue by immunohistochemistry. (Cohort 1 and 2)

2.34 To correlate tumor response (RECIST 1.1) with the phenotype and frequency of key leukocyte subsets (i.e., PD-1+ T cells, Tregs, myeloid subsets) in the peripheral blood before, at 6 and 18 weeks on therapy, and at 54 weeks (study completion), PD, or study withdrawal. Peripheral blood mononuclear cells and neutrophils will be isolated concomitantly by density gradient from peripheral blood, cryopreserved, and analyzed by 10-color flow cytometry. (Cohort 1)

2.35 To correlate tumor response (RECIST 1.1) with PD-1+ T cell functional capacity. Stimulated cytokine assays will be performed on lymphocyte populations isolated from peripheral blood, as described in 2.34. Briefly, cells will be stimulated with PMA/ionomycin or plate-bound anti-CD3 plus soluble anti-CD28 for 6 hours in the presence of brefeldin A and intracellular expression levels of IL-2, IFNγ, and TNFα will be determined by flow cytometry**.** Normal peripheral blood will be used as a control for optimal cytokine production. Patient T cell function will be compared before and after treatment. (Cohort 1)

2.36 To correlate tumor response (RECIST 1.1) with serum anti-thyroglobulin antibody levels assessed before, and at 18 weeks on therapy . (Cohort 1 and 2)

2.37 To correlate tumor response (RECIST 1.1) with tumor mutation status. Tumor mutation analysis will be performed by whole exome sequencing with DNA isolated from pre-treatment frozen biopsies and FFPE archival primary tumor for each patient where available, using patient-matched blood as a baseline control. (Cohort 1)

2.38 To broadly investigate mechanisms of response and resistance to combination therapy, gene expression profiles will be generated from frozen biopsies for analysis by RNA-Seq. Total RNA will be isolated with the RNeasy kit (Qiagen) and 500ng of RNA will be submitted mRNA-seq library construction (TruSeq Stranded mRNA Library Kit, Illumina). In parallel, FFPE primary tumor samples will be analyzed by RNA-Seq (Graw S, et. al., 2015)[40]. (Cohort 1)

3.0 Patient Eligibility

*No waivers of eligibility per ACCRU

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Locally recurrent and unresectable and/or distant metastatic differentiated thyroid cancer (DTC), histologically or cytologically confirmed. The diagnosis of DTC includes the following subtypes: Papillary thyroid cancer (PTC) (including but not limited to variants such as follicular variant, tall cell, columnar cell, Hürthle cell variant of papillary carcinoma, and poorly differentiated), Follicular thyroid cancer (FTC), including Insular variant, Hürthle cell carcinoma and poorly differentiated thyroid cancer.

3.13 Measurable disease meeting the following criteria (see Section 11.0):

3.13a At least 1 lesion of ≥ 1.0 cm in the longest diameter for a non-lymph node or ≥ 1.5 cm in the short-axis diameter for a lymph node which is

serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI). If there is only one target lesion and it is a non-lymph node, it should have a longest diameter of ≥ 1.5 cm.

3.13b. Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

3.14 For Cohort 1 Only: Evidence of disease progression ≤14 months prior to registration according to RECIST 1.1, as confirmed by the site study PI.

3.15 For Cohort 2 Only: Progressive disease (PD) on lenvatinib per RECIST 1.1 ≤60 days prior to registration, as confirmed by the site study PI. Patients need to have documented imaging and measurement of RECIST target lesions within 30 days of starting pembrolizumab.

3.16 Radioiodine (RAI)-resistant disease as defined by one or more of the following criteria:

a. One or more measurable lesions that do not demonstrate RAI uptake

b. One or more measurable lesions progressive by RECIST 1.1 ≤14 months of prior RAI therapy.

c. One or more measurable lesions present after cumulative RAI dose of ≥ 600 mCi.

d. One or more measurable lesions that are FDG-avid (>5 SUV), if PET/CT scan performed. These lesions may also be RAI-avid.

3.17 ECOG Performance Status (PS) 0 or 1. (Form is available on the ACCRU web site)

3.18 The following laboratory values obtained ≤30 days prior to registration, unless otherwise specified:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or erythropoietin dependency (≤7 days prior to registration)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

3.19a Adequately controlled blood pressure with or without antihypertensive medications defined as BP < 150/90 mmHg at screening.

3.19b Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.19c Ability to complete Patient Medication and Blood Pressure diaries by themselves or with assistance.

3.19d Willing and able to provide informed written consent.

3.19e Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19f Willing to provide tissue and blood samples for correlative research purposes.(see Sections 6.12, 14.1 and 17.11).

3.2 Exclusion Criteria

3.21 **Cohort 1 only**: Prior treatment with previous VEGFR active multikinase inhibitor.

3.22 **Cohort 2 only**: Discontinued lenvatinib due to toxicity.

3.23 Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.24 Female subjects of childbearing potential: Unwilling or unable to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. NOTE: Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

3.25 Male subjects: Unwilling or unable to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

3.26 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.27 Immunocompromised patients and patients known to be HIV positive (HIV 1/2 antibodies) and currently receiving antiretroviral therapy.

3.28 Currently participating and receiving study therapy (except lenvatinib for patients in Cohort 2) or has participated in a study of an investigational agent and received study therapy within 4 weeks prior to registration.

3.29a Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy ≤7 days prior to the first dose of trial treatment.

3.29b Known history of active TB (Bacillus Tuberculosis)

3.29c Hypersensitivity to pembrolizumab or any of its excipients.

3.29d Prior anti-cancer monoclonal antibody (mAb) ≤4 weeks prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered ≥4 weeks prior to registration.

3.29e Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 (except lenvatinib for patients in Cohort 2) or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

NOTE:

- Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to registration, as deemed by treating investigator or site PI.

3.29f Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

3.29g Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. NOTE: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for ≥7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3.29h Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). NOTE: Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.29i Known history of, or any evidence of active, non-infectious pneumonitis that required steroids.

3.29j Active infection requiring systemic therapy.

3.29k History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.29l Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.29m Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3.29n Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.29o Received a live vaccine ≤30 days of planned start of study therapy. NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.29p Proteinuria >1+ on dipstick urinalysis. Patients with >1+ proteinuria on dipstick urinalysis will undergo 24-hour urine collection for quantitative assessment. NOTE: Patients with > 1 g/24 hours will be ineligible.

3.29q Clinically significant gastrointestinal malabsorption syndrome.

3.29r New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia associated with significant cardiovascular impairment within the past 6 months. EF by MUGA or echo should not be less than the institutional lower limit of normal.

3.29s QTc prolongation > 480 msec, as calculated by either the Bazett or Fridericia formula, as per institutional standard.

3.29t Active hemoptysis (bright red blood > 1 teaspoon on more than one occasion) ≤3 weeks prior to registration.

3.29u **Cohort 2 only:** More than one prior treatment with VEGFR active multikinase inhibitor prior to original start of lenvatinib.

4.0 Test Schedule

Additional testing and monitoring can be done as clinically indicated.

Tests and Procedures	**Active Monitoring** Cycles = 21 days Study visits and tests may occur +/- 3 days										
	≤30 days prior to reg.	Prior to treatment initiation	Cycle 1, Day 1	Cycle 2,4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 24*, 26*, 28*, 29*, 30*, 32* and 34* Day 1	Cycle 3, day 1	Cycle 7, day 1, Cycle 19 day 1, (or at PD or withdrawal)	Cycle 7 day 1	Cycles 5,7, 11, 15 and 19, 23,* 27,* 31,* 35,* Day 1	Cycles 9, 13, 17, 25* and 33,* Day 1	At PD, withdrawal, removal, or study completion	Observation † every 3 months for 3 years or until PD
History and exam, wt, BP[1], ECOG PS	X		X	X	X			X	X	X	X
Height	X										
Adverse event assessment[10]	X			X	X			X	X	X	X
Hematology: CBC/ differential, PT/INR[2], PTT[2]	X		X	X	X			X	X	X	X
Chemistries: SGOT (AST), SGPT (ALT), alb, alk phos, T. bili, D. bili, albumin, BUN, CL, CO2, creatinine, calcium, phos, glucose, Na, K, Mg	X		X	X	X			X	X	X	X
TSH, free T4, thyroglobulin	X[4]				X[4]			X[4]			
Urinalysis[9]	X			X	X			X	X	X	X
Pregnancy test	X[3]										

MUGA or Echocardiogram	X								X		
EKG	X				X				X		
Tumor measurement	X				X[5]			X[5]			X[5]
Mandatory blood sample (Cohort 1; see Section 14.0)		X[R, 6]			X[R, 6]	X[R, 6]				X[R, 6]	
Mandatory blood sample (Cohort 2)		X[12]									
Mandatory serum sample (Cohorts 1 and 2; see Section 14.0)		X[R, 6]					X[R, 6]				
Mandatory archival surgical tissue sample (Cohorts 1 and 2; see Section 17.3)	X[R, 7]										
Optional tissue biopsy (Cohort 1; see Section 17.3)		X[R, 8]									
Patient Medication Diary			X[11]	X[11]	X[11]			X[11]	X[11]	X[11]	
Patient Blood Pressure Diary			X[11]	X[11]	X[11]			X[11]	X[11]	X[11]	

† Observation Phase: Part of the Active Monitoring Phase of a study. The time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule. Participants will be required to return to the consenting site for follow-up. Time frame is +/- two weeks.

* Cycles 23 – 35 apply only to those patients who extend treatment for up to an additional 12 months beyond the initial 54-week treatment period.

[1] Patients should be instructed to monitor BP at home three times/week at a minimum, and notify treating team if systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg.

[2] PT/INR and PTT are only necessary at baseline, and as clinically indicated.

[3] For women of childbearing potential only. Must be done ≤ 7 days prior to registration. This can be done by either blood or urine test, at the physician's discretion.

[4] Check TSH and free T4 at baseline, then every other cycle starting with Cycle 3 then cycles 5 & 7 (day 1), then every 4th cycle starting with Cycles 11, 15 and 19 (day 1)for up to 54 weeks for all patients. For those patients who continue treatment beyond 54 weeks (up to an additional 12 months), continue checking TSH and free T4 on cycle 23, 27, 31 and 35. For those patients who do NOT have anti-thyroglobulin antibodies, check thyroglobulin at baseline, and then same time points as TSH and free T4.

[5] Imaging is to be performed day 1 for Cycles 3, 5, and 7, then every 4th cycle for Cycles 11, 15, and 19, up to 54 weeks. Scans can be done sooner than 18 weeks if clinically indicated. (See Section 13 for further details.) For those patients who continue treatment beyond 54 weeks (up to an additional 12 months), imaging should be done on Cycle 23, 27, 31 and 35. CT or MRI scans of the neck, chest, abdomen and pelvis, as determined by the investigator to assess response per RECIST v1.1. Imaging with IV contrast is encouraged but will be done per investigator's discretion. If the abdomen-pelvic CT is negative at baseline, subsequent imaging of this site is required only if clinically indicated during the study period. NOTE: Use same imaging throughout the study as much as possible. PET scans are performed only as clinically indicated at pre-study, and for restaging as determined per investigator's discretion. For those patients who have initial progression (PD) in the first 12 weeks post-registration, a confirmation scan will be required 4 weeks later to confirm PD. See 13.6 for further details. If progression is confirmed then the date of disease progression will be the first date the patient met the criteria for progression based on standard RECIST 1.1 criteria.

[6] Mandatory blood draws for research immunology studies should *not* be collected and submitted until *after* the patient is registered onto the study, but before beginning study treatment, Cycle 3, Cycle 7 and Cycle 19 or PD, withdrawal, removal, or study completion for peripheral blood mononuclear cells (PBMC) (4 times), and for serum before treatment and cycle 7 day 1 (2 times). See Section 14 and Laboratory Manual for detailed information regarding blood draws.

[7] ≤60 days from registration. NOTE: Receipt of archival tumor tissue is not required for study registration and initiation of therapy. (Cohort 1 and 2)

[8] CT-guided or ultrasound-guided tumor biopsy *after* the patient is registered onto the study, but *before* beginning study treatment. Collection of this tissue is optional for research purposes. If a patient is not willing to undergo this procedure, it does not cause the patient to be ineligible; however, collection of this tissue is **strongly encouraged** (Cohort 1; anticipate collecting samples from 20 of 30 patients)

[9] Patients with >1+ proteinuria on dipstick urinalysis will undergo 24-hour urine collection for quantitative assessment. Patients with > 1 g/24 hours on the baseline assessment will be ineligible. See Section 8.22 for management of proteinuria.

[10] Adverse events should be assessed at every cycle and are done prior to infusion of pembrolizumab.

[11] Patients' blood pressure diary and patient medication diary should be given to the patient on day 1 of each cycle.

[12] The mandatory blood sample for Cohort 2 can be drawn at any time after registration. For new patients, it must be drawn prior to the study treatment initiation. For patients who have started treatment, it must be drawn at the next treatment visit. Submit the Specimen Submission: Blood (PBMC for Cohort 2 only) Form in Rave via Add Event drop down box.

[R] Research funded (see Section 19.0)

5.0 Grouping Factor:

- Cohort 1 vs. 2

6.0 Registration Procedures

6.1 Registration Procedures

6.11 To register a patient, access the ACCRU web page at [redacted] , go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted] click on "Registration, Installation & Entry Instructions".

6.12 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19f, 14.1 and 17.11).

Cohort 1 only: An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.11).

- Patient has/has not given permission to give his/her tissue sample for optional correlative research testing planned as part of this study.

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

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

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

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

- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her tissue sample(s) to outside researchers.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her blood sample(s) to outside researchers.

6.16 Treatment cannot begin prior to registration and must begin ≤10 days after registration.

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

6.18 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.19a Treatment on this protocol must commence at an ACCRU institution under the supervision of the treating physician who is either study site's principal investigator or co-investigator.

6.19b Study drug is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule

Arm	Agent	Dose Level	Route	Day
	Lenvatinib	20 mg	PO	Once daily Days 1 through 21 of each 21-day cycle
	Pembrolizumab	200 mg	IV	Day 1 of each 21-day cycle

7.11 Cohort 1: Lenvatinib-naïve patients will be administered both study drugs (pembrolizumab and lenvatinib) as of Cycle 1 Day 1. Each cycle is 21 days. The starting dose of oral lenvatinib is 20 mg (two 10-mg capsules).

7.12 Cohort 2: Pembrolizumab will be added to the treatment for patients who experience PD on lenvatinib alone. They will remain on or resume the dose of lenvatinib on which they experienced PD. Cycle 1 Day 1 will be the first day pembrolizumab is added to the treatment. Patients who have temporarily stopped lenvatinib dosing within 30 days of enrollment will restart lenvatinib at their prior dose along with pembrolizumab on Cycle 1 Day 1 of treatment.
Patients entering Cohort 2 will have progressed on lenvatinib. These patients will remain on the dose they are taking at the time of study entry, which may have been previously reduced for side effect management, and will not exceed 20 mg by mouth daily.

7.2 Patients will be instructed on lenvatinib administration, to be taken with water orally once a day (with or without food) at approximately the same time each day, and granted treatment independence with nursing staff approval. If a patient misses a dose, and cannot be taken within 12 hours, then that dose should be omitted and the next dose should be taken at the usual time of administration. If a patient vomits after taking the daily dose of lenvatinib, DO NOT repeat dosing. Resume regular dosing the next day. NOTE: The patient will be requested to maintain a medication diary to document time and date when each dose of lenvatinib is taken. Patient will also document number of pills/dose of medication taken, and note any vomiting subsequent to dosing. The medication diary will be returned to clinic staff at each examination visit (see Section 4.0).

7.3 Pembrolizumab, 200 mg, will be administered as a 30-minute IV infusion every 21 days (treatment cycle intervals may be increased based on toxicities as described in section 8.3). Sites should target infusion timing to be as close to 30 minutes as possible, however, given the variability of infusion pumps from site to site, a window of -5 and +10 minutes is permitted (i.e., infusions lasting between 25 minutes to 40 minutes are acceptable).

7.4 Study treatment with pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

7.5 For this protocol, the patient must return to the consenting ACCRU institution for evaluation day 1 of cycles 2, 3, 5, 7, 9, 11, 13, 15, 17 and 19 (see Section 4.0 Test

Schedule, Active Monitoring Phase).

7.6 Treatment with study-specific drugs by a local medical doctor (LMD) is not allowed.

7.7 Patients who develop PD in the CNS only may receive radiotherapy and continue treatment on study after completion of radiotherapy. Patient must be clinically stable and have been off systemic corticosteroids for at least 14 days at the time of recommencement of treatment. **NOTE: Both lenvatinib and pembrolizumab should be withheld for a minimum of 3 days prior to radiation and for 3 weeks after radiation.**

7.8 Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients receiving treatment in this study will be permitted to continue treatment beyond initial PD, if the initial PD happens in the first 12 weeks post-registration (by RECIST 1.1), as long as they meet the following criteria:

- Investigator-assessed clinical benefit (e.g. absence of rapid disease progression and absence of progressive tumor at a critical anatomic site that requires urgent alternative intervention), and
- The patient is tolerating study drug.
- Patient does not continue to progress at 4 week follow-up imaging after PD first noted.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to address side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Tables 8.2 and 8.3)

Dose Level	Lenvatinib[a]	Pembrolizumab
0[b]	20 mg orally once a day	200 mg IV every 21 days
-1	14 mg orally once a day	No dose reduction allowed
-2	10 mg orally once a day	No dose reduction allowed
-3	4 mg orally once a day	No dose reduction allowed

[a] Once the dose has been reduced, it should not be increased at a later date.

[b] Dose level 0 refers to the starting dose.

8.2 Dose Modifications for **Lenvatinib**-Related Toxicities

Treatment-Related Toxicity[a, b] including hepatic injury and venous thromboembolic events	**Management**	**Dose Modification**
Grade 1 and Tolerable Grade 2		
	Continue Treatment	No change
Intolerable Grade 2[c] or Grade 3[d, e]		
First occurrence	Hold until resolved to Grade 0-1 or baseline[f]	14 mg orally once a day
Second occurrence (same toxicity or new toxicity)	Hold until resolved to Grade 0-1 or baseline[f]	10 mg orally once a day
Third occurrence (same toxicity or new toxicity)	Hold until resolved to Grade 0-1 or baseline[f]	4 mg orally once a day
Fourth occurrence (same toxicity or new toxicity)	Hold until resolved to Grade 0-1 or baseline[f]	Contact ACCRU Quality Assurance Specialist
Grade 4[g]: Discontinue Study Treatment		

NOTE: See CTCAE v4 for grading:

[redacted]

Collect all CTC grades of AEs, decreasing and increasing grade.

a. A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the ACCRU Quality Assurance Specialist before treatment can be resumed (see protocol resource page).

b. Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment, interruption, or dose reduction.

c. Grade 2 toxicities will be determined to be tolerable or intolerable by both the subject and investigator. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.

d. Weight loss of any grade may not require dose reduction, but should be managed based on the judgment of the investigator. Subjects with weight loss requiring dose interruption and reduction do not need to return to baseline weight to restart lenvatinib. Based on the judgment of the investigator, subjects may be restarted at a lower dose of lenvatinib for weight loss. Consultation with a registered dietician may be helpful in managing weight loss.

e. Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator (e.g., ALT, AST, γ-GTP values < 10 × ULN, and Na).

f. For hematology toxicities, restart treatment after toxicity resolves to Grade ≤ 2.

g. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

8.21 Management of Hypertension

Hypertension is a known and potentially serious adverse event associated with lenvatinib treatment. Patients will be given a Blood Pressure Diary (Appendix III) on which to record their measurements. They should be instructed to check their blood pressure at least three times each week, and notify the treating physician if systolic BP ≥160 mmHg and/or diastolic BP ≥ 100 mmHg.

The following guidelines should be followed for the management of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg confirmed on repeat measurements after an hour:

Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving this.

For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.

If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a dose of 14 mg once daily (or one dose level reduction) when systolic BP ≤ 150 mmHg and diastolic BP ≤ 95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 20-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 14 mg once daily (one dose level reduction) only when systolic BP ≤ 150 mmHg and diastolic BP ≤ 95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 14-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 10 mg once daily (one dose level reduction) only when systolic BP ≤ 150 mmHg and diastolic BP ≤ 95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 10-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 4 mg once daily (one dose level reduction) only when systolic BP ≤ 150 mmHg and diastolic BP ≤ 95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

Additional dose reduction should be discussed with the ACCRU SAE

Coordinator (see protocol resource page).

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue lenvatinib

8.22 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Test Schedule (Section 4.0).

Guidelines for assessment and management of proteinuria:

A 24-hour urine collection for protein quantitation **is required** in the following situations:

- The first (initial) occurrence of 2+, 3+, or 4+ proteinuria on urine dipstick while on study drug
- A subsequent apparent increase in severity of urine dipstick proteinuria (from the prior measurement which was ≥2+) occurring on the same lenvatinib dose level
- When there has been a lenvatinib dose reduction and on follow-up, the urine protein dipstick result is 2+, 3+, or 4+ (at the new dose level)

The 24-hour urine collection **is <u>not</u> required** in the following situations:

- Persistence of the same severity of proteinuria by urine dipstick at the same lenvatinib dose level (when a 24-hour urine collection has already been collected at that dose level)
- Subsequent occurrences of 2+, 3+, or 4+ proteinuria by urine dipstick when the subject has been off study drug

Grading of proteinuria should be performed according to CTCAE v4.03 (Appendix 3) BUT will be based on the 24-hour urine collection for total protein result, if a 24-hour urine was performed at that time point.

For subjects with lenvatinib-related toxicity, the dose reduction and/or interruption instructions provided in Table 2 of the study protocol should be followed.

8.23 Management of Hepatotoxicity

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 8.2, "Dose Modifications for **Lenvatinib**-Related Toxicities" should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, lenvatinib must be discontinued.

8.24 Management of Venous and Arterial Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, signs of deep vein thrombosis including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a venous thromboembolic event is confirmed, instructions contained in Table 8.2, "Dose Modifications for **Lenvatinib**-Related Toxicities" should be followed. Appropriate supportive care should be provided together with close monitoring.

If a subject experiences any arterial thromboembolic event, lenvatinib must be discontinued.

8.25 Management of Posterior Reversible Encephalopathy Syndrome

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder, which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES, dose interruptions, dose adjustments, or discontinuation may be required as per instructions included in Table 8.2.

8.26 Management of Hypocalcemia

Serum calcium should be monitored per the Test Schedule (Section 4). Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

8.27 Management of Myocarditis

8.27a LVEF normal/nonmalignant rhythm- Obtain cardiology consultation, review case with overall study PI, and consider 1 gram IV solumedrol daily for 3-5 days (consider mycophenolate vs IVIG vs cyclosporine vs plasmapheresis for persistent myocarditis).

8.27b LVEF reduced or patient is unstable- Obtain a cardiology consultation and review the case with overall study PI.

8.3 Dose Modifications for **Pembrolizumab**-Related Toxicities

CTCAE System/Organ/Class (SOC)	**Adverse Event**	**Hold Treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**
Gastrointestinal Disorders	Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue
Endocrine Disorders	Other: Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
Immune System Disorders	Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Investigations	AST, ALT or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
		3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Metabolism and Nutrition Disorders	Type 1 Diabetes Mellitus (if new onset) or Hyperglycemia	TIDM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subject is clinically and metabolically stable.
	Hypercalcemia	3-4	Toxicity resolves to Grade 0-1	Resume pembrolizumab when subject is clinically and metabolically stable.

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal and urinary disorders	Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
		3-4	Permanently discontinue	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
		3-4	Permanently discontinue	Permanently discontinue
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently Discontinue		
	All Other Drug-Related Toxicity[b]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue

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

a. For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.
b. Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

8.4 Treatment Guidelines for Subjects Who Experience an Infusion Reaction Associated with the Administration of **Pembrolizumab**

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

Infusion Reaction Treatment Guidelines for Pembrolizumab		
CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further study treatment administration.**	No subsequent dosing.
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

9.0 Additional Supportive Care

9.1 Antiemetics and intravenous fluids may be used at the discretion of the treating physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow the published Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 2015;33:3199-3212.

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

9.4 Diarrhea/Colitis:

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

All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

For **Grade 3 or 4 diarrhea/colitis** that persists >1 week, treat with intravenous steroids followed by high dose oral steroids.
When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

9.6 Apart from the assigned study drugs, subjects are **prohibited from receiving the following therapies** during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

9.61 Antineoplastic systemic chemotherapy or biological therapy

9.62 Immunotherapy not specified in this protocol

9.63 Chemotherapy not specified in this protocol

9.64 Investigational agents other than pembrolizumab and lenvatinib

9.65 Radiation therapy. NOTE: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

9.66 Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

9.67 Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the ACCRU Quality Assurance Specialist (see protocol resource page).

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

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

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

9.7 Pneumonitis:

For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional antiinflammatory measures, as needed. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

9.8 Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

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

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

9.9 Hypophysitis:

For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

9.9a Additional Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as

additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

9.9a1 Hepatic:

For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

- Treat with IV or oral corticosteroids

For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

9.9a2 Renal Failure or Nephritis:

For **Grade 2** events, treat with corticosteroids.

For **Grade 3-4** events, treat with systemic corticosteroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.9a3 Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

10.0 Adverse Event (AE) Reporting and Monitoring

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

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

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

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

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

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

Routine Reporting
Events reported to sponsor via case report forms

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

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used 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:
[redacted]

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

b. Identify the grade and severity of the event using the CTCAE version 4.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

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

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

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

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

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

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

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

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

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.32 **Special Situations for Expedited Reporting**

EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.5). *

System Organ Class (SOC)	**Adverse event/ Symptoms**	**CTCAE Grade at which the event will *not* be *expeditedly* reported.**
Generalized disorders and administration site conditions	Fatigue	≤Grade 3
Gastrointestinal disorders	Diarrhea	≤Grade 3
	Abdominal pain	≤Grade 3
	Vomiting	≤Grade 3
	Constipation	≤Grade 3
	Mucositis oral	≤Grade 3
	Nausea	≤Grade 3
Investigations	Weight loss	≤Grade 3
	Increased AST	≤Grade 3
Metabolism and nutrition disorders	Loss of appetite	≤Grade 3

Musculoskeletal and connective tissue disorders	Myalgia	≤Grade 3
Nervous system disorders	Headache	≤Grade 3
Renal and urinary disorders	Proteinuria	≤Grade 3
Respiratory, thoracic and mediastinal disorders	Cough	≤Grade 3
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia	≤Grade 3
	Pruritis	≤Grade 3
	Rash maculo-papular	≤Grade 3
Vascular disorders	Hypertension	<Grade 3

*These exclusions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

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

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

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

Efficacy endpoints as outlined in this section will not be reported to Merck or Eisai as described in Section 10.4 - Immediate Reporting of Adverse Events to the ACCRU and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the ACCRU within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

ACCRU will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety

[redacted] as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g., transportation issues etc.) will not be considered a SAE.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.321 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
    - **Reportable categories of Death:** Death attributable to a CTCAE term.
    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
    - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.322 Secondary Malignancy

- A ***secondary*** malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy

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

10.323 Second Malignancy

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

10.324 Pregnancy

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

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

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

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of study drugs, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole,

blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above.

Such events must be reported within 24 hours to the Sponsor and within 2 business days to Merck Global Safety [redacted]

Use the ACCRU Expedited Report Form, found on the ACCRU web site ([redacted]). NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour / 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour / 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Follow site-specific reporting guidelines.

Submit the ACCRU Adverse Event Expedited Report Form to ACCRU Safety via email at: [redacted] ACCRU Safety will forward to Merck [redacted]

ACCRU Safety will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

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

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation. (Grading is not necessary in the absence of these conditions.) This list includes but is not limited to the symptoms/conditions listed below. The CTCAE v4.0 grading should be used:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Generalized	Fatigue	X	X
Gastrointestinal	Diarrhea	X	X
Cardiovascular	Hypertension	X	X
Renal	Proteinuria	X	X
Generalized	Weight loss	X	X
Renal	Acute kidney injury	X	X
Pulmonary	Pneumonitis	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU) Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable).

10.54 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.531 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

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

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

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

10.56 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the ACCRU SAE Coordinator using the ACCRU Adverse Event Expedited Report Form. Within 2 working days, the ACCRU SAE Coordinator will report to Merck Global Safety. [redacted]

[redacted]

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

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

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined below that is not associated with clinical symptoms or abnormal laboratory results.

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

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the ACCRU SAE Coordinator using the ACCRU Adverse Event Expedited

Report Form. Within 2 working days, the ACCRU SAE Coordinator will report to Merck Global Safety. [redacted]

11.0 Treatment Evaluation Using RECIST Guideline

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

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

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 6 weeks to 18 weeks after treatment initiation, then every 12 weeks until end of active study treatment (54 weeks). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

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

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

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

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

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

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

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

11.32 Acceptable Modalities for Measurable Disease:

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

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: 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.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is

considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained ≥4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 4 weeks (see Section 11.44).

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

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

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

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

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

11.43 Response Criteria

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

Note: Non-target lesions and non-target lymph nodes should be

evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

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

  a. Disappearance of all target lesions.

  b. Each target lymph node must have reduction in short axis to <1.0 cm.

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

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

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

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

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

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

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

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

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

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

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

11.44 Overall Objective Status

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

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

*See Section 11.431

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

Note: For those patients who have initial PD in the first 12 weeks post-registration, a confirmation scan will be required 4 weeks later to confirm PD. See Section 13.7 for further details. If progression is confirmed then the date of disease progression will be the first date the patient met the criteria for progression based on standard RECIST 1.1 criteria.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Region: North America vs. Europe

12.2 Disease TNM stage at diagnosis: I vs. II vs. III vs. 4A vs. 4B vs. 4C

12.3 History of lymphocytic thyroiditis: Yes vs. No

12.4 Prior systemic VEGFR-active kinase inhibitor therapy: Yes vs. No

12.5 Histologic subtype of primary tumor: papillary vs. follicular variant vs. follicular vs. Hurthle or poorly differentiated

12.6 Sites of metastatic lesions: none vs. nodal vs. pulmonary vs. bone vs. liver vs. CNS/brain vs. subcutaneous tissue vs. other

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy or refuse treatment or choose alternative therapy will go to the event-monitoring phase per Section 18.0 and be followed every 180 days for a maximum of 3 years from study registration. (See exceptions in 13.5 and 13.6.)

13.3 Patients who go off protocol treatment for reasons other than those listed in Section 13.2 above (e.g., adverse events, other complicating disease) will go to Observation and will follow the test schedule (Section 4.0) every 84 days for a maximum of 3 years from study registration. If they progress or choose alternative therapy while in Observation, they will go to the event-monitoring phase.

13.4 OBSERVATION: The study treatment period is 54 weeks (19 cycles). Patients who are receiving clinical benefit (i.e., in CR or PR or SD) and who are tolerating treatment at the end of the study treatment period may continue on therapy for an additional 12 months. After study treatment has been discontinued, they should be observed every 12 weeks until PD or a maximum follow-up of 3 years from study registration. Once the patient has PD during observation, they will be followed in the event-monitoring phase for a maximum follow-up of 3 years from study registration (see Section 18.0). Subsequent treatment is at the discretion of their attending physician. NOTE: If the patient continues for an additional 12 months of treatment beyond the initial 54 weeks, the patient should follow the same test schedule, per protocol, as is done during the initial 54-week period.

13.5 Patients who develop PD in the CNS may receive radiotherapy and continue treatment on study after completion of radiotherapy. **NOTE: Both lenvatinib and pembrolizumab should be withheld for a minimum of 3 days prior to radiation and for 3 weeks after radiation.**

13.6 Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients receiving treatment in this study will be permitted to continue treatment beyond initial PD, if the initial PD happens in the first 12 weeks post-registration (by RECIST 1.1), as long as they meet the following criteria:

- Investigator-assessed clinical benefit (e.g. absence of rapid disease progression and absence of progressive tumor at a critical anatomic site that requires urgent alternative intervention), and
- The patient is tolerating study drug.
- Patient does not continue to progress at 4 week follow-up imaging after PD first noted.

Patients with initial progression will be assessed with clinical judgment as to whether the patient is deriving clinical benefit from treatment and should continue study treatment or discontinue and enter the follow up/survival phase of the study. If progression is confirmed then the date of disease progression will be the first date the patient met the criteria for progression based on the standard RECIST 1.1 criteria.

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

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

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

13.9 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and Off-Treatment Form must be submitted. Event monitoring will be required per protocol (Section 18.0).

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol
NOTE: Please refer to study specific Laboratory Manual.

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Prior to Treatment Initiation[3]	Cycle 3, Day 1, Cycle 7, Day 1, Cycle 19 day 1, and at PD, study completion, or time of withdrawal or removal	Cycle 7, Day 1	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
Mandatory (Cohort 1)	BD Vacutainer Cell Preparation Tube with sodium citrate (CPT; light blue/black)	8 ml; up to 24 ml total (3)	PBMC[2]	X	X		Yes, Process within 2 hours of collection	Frozen/Dry Ice ***or*** Cryopreservation /Liquid Nitrogen
Mandatory (Cohort 2)	BD Vacutainer Cell Preparation Tube with sodium citrate (CPT; light blue/black)	8 ml; up to 24 ml total (3)	PBMC[2]	X			Yes, Process within 2 hours of collection	Frozen/Dry Ice ***or*** Cryopreservation /Liquid Nitrogen
Mandatory (Cohorts 1	BD Vacutainer	7.5 ml (1)	Serum	X		X	Yes, Process	Frozen/Dry ice

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Prior to Treatment Initiation[3]	Cycle 3, Day 1, Cycle 7, Day 1, Cycle 19 day 1, and at PD, study completion, or time of withdrawal or removal	Cycle 7, Day 1	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
and 2)	Serum Separator Tube (SST; red/gray)						within 2 hours of collection	

1. Kits should be ordered using the Biospecimen Kit Order Form found on the ACCRU web site. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.215 and Laboratory Manual for detailed shipping instructions.)
2. Individual sites will run a density gradient with Ficoll-Hypaque gradient that is supplied in the Cell Preparation Tubes (CPT). This will give a PBMC layer in each of the 3 tubes that can be combined in the same cryopreservation tubes.
3. Mandatory blood draw is collected once any time after study registration. For new patients, it must be drawn prior to the study treatment initiation. For patients who have started treatment, it must be drawn at the next treatment visit. Submit the Specimen Submission: Blood (PBMC for Cohort 2 only) form for this blood draw in Rave via Add Event drop down box.

14.2 Study Methodology and Storage Information

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

NOTE: research blood samples should not be collected and submitted until *after* the patient is registered onto the study, but *prior* to beginning study treatment.

14.211 The peripheral blood mononuclear cells (PBMC) will be isolated by density gradient from approximately 24ml peripheral blood. In Cohort 1, Samples will be collected before treatment, Cycle 3 Day 1, Cycle 7 Day 1 and Cycle 19 Day 1, or time of withdrawal or removal. In Cohort 2, a single blood draw will be performed pretreatment or at any point during the study in order to generate a source of normal DNA. PBMC will be washed and cryopreserved for later analysis by flow cytometry and as a source of normal control DNA. Cells will be aliquoted in cryopreservation media, frozen at -80°C and shipped overnight on dry ice. For long-term storage, frozen cells will be stored in liquid nitrogen and shipped on liquid nitrogen. (See Laboratory Manual, Cohort 1)

14.212 Serum will be isolated from blood for analysis of TPO and Tg autoantibody levels. Samples will be collected before treatment and on Day 1 of Cycle 7. Autoantibody levels will be run at the University of Colorado Hospital (UCH) providing uniform testing in a CLIA accredited clinical laboratory. The Siemens ADVIA Centaur XP anti-TPO assay at UCH has an analytical sensitivity of 28 U/mL and a dynamic range of 28–1300 U/mL. The Beckman Coulter Access Thyroglobulin Antibody II assay at UCH has an analytical sensitivity of 0.9 IU/mL and a dynamic range of 0.9-2500 IU/mL. Baseline autoantibody status (positive or negative) and titer as well as autoantibody level changes over the treatment period will be correlated with response to therapy. Serum will be isolated from 7.5 mL of blood, aliquoted into 4 cyrovials, and frozen at -80°C for 48 hours before shipping overnight on dry ice (See Laboratory Manual, Cohorts 1 and 2)

14.213 DNA and RNA will be extracted from peripheral blood to generate a baseline control for the studies detailed in Section 17. Remaining DNA and RNA will be stored frozen at -80ºC at the University of Colorado, according to patient consent information (see Section 6.12) until specific analyses are identified. As protocols are developed, they will be presented for ACCRU, ITOG, and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.214 As part of ongoing ACCRU research, remaining serum will be stored frozen at -80ºC at University of Colorado, according to patient consent information (See Section 6.15) for future studies until specific analyses are identified. As protocols are developed, they will be presented for ACCRU, ITOG and IRB review and approval.

14.215 Shipment of samples: Please refer to the Laboratory Manual.

14.3 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND #132069

15.1 **Lenvatinib (LENVIMA®)**

- Investigator brochure is available on the ACCRU web site.

15.11 **Background**: Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor (PDGF) receptor PDGFRα; KIT; and RET.

15.12 **Formulation**: Lenvatinib is available as 1 mg, 4 mg and 10 mg capsules. The following are inactive ingredients: Calcium Carbonate, USP; Mannitol, USP; Microcrystalline Cellulose, NF; Hydroxypropyl Cellulose, NF; Hydroxypropyl Cellulose (type H), NF; and Talc, USP. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

15.13 **Preparation and storage**: Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F).

15.14 **Administration:** Take lenvatinib at the same time each day with or without food. The capsules should be swallowed whole with water. If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be omitted and the next dose should be taken at the usual time of administration.

Alternatively, add the lenvatinib capsules to a tablespoon of water or apple juice in a small glass to produce a suspension. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

This can also be administered by gastric feeding tube.

15.15 **Pharmacokinetic information**:

Absorption: Lenvatinib is rapidly absorbed after oral administration with tmax typically observed from 1 to 4 hours post dose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered to healthy subjects with food, peak plasma concentrations are delayed by 2 hours.

Distribution: In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 – 30 μg/mL, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin. In vitro blood to plasma ratios of lenvatinib (0.1 - 10 μg/mL) remained constant in humans (0.589 – 0.608).

Metabolism: Lenvatinib is extensively metabolized in humans. The main metabolic pathways in humans were identified as oxidation by AO, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (eg, glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerization).

Half-life elimination: Plasma concentrations decline bi-exponentially following Cmax. The terminal exponential half-life of lenvatinib is about 28 hours.

Excretion: Following administration of radiolabeled lenvatinib to 6 subjects with solid tumors, approximately two-thirds and one-fourth of the radiolabel were eliminated in the feces and urine, respectively.

Special populations: No dose adjustments are required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, the starting dose should be lowered. No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the starting dose should be lowered. Further dose adjustments may be necessary on the basis of individual tolerability.

15.16 **Potential Drug Interactions**: In vitro, cytochrome P450 3A4 was the predominant (>80%) cytochrome isoform involved in the P450-mediated metabolism of lenvatinib. In vivo, inducers and inhibitors of CYP3A4 had a minimal effect on lenvatinib exposure. Lenvatinib is not considered a strong inducer or inhibitor of cytochrome P450 or uridine 5′-diphospho-glucuronosyl transferase (UGT) enzymes. Lenvatinib may be co-administered without dose adjustment with CYP3A, P-glycoprotein (P-gp), and BCRP inhibitors or CYP3A and P-gp inducers.

15.17 **Known potential toxicities**:

Common and less common known potential toxicities, ≥ 1%

Gastrointestinal: Abdominal pain, diarrhea, diarrhea nausea, vomiting,
General and administrative site conditions: Asthenia
Metabolism and nutrition disorders: Decreased appetite, dehydration
Renal and urinary disorders: Acute kidney injury
Respiratory thoracic, and mediastinal disorders: Pulmonary embolism
Vascular disorders: Hypertension, hypotension

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

Blood and lymphatic disorders: Thrombocytopenia
Cardiac disorders: Acute myocardial infarction, cardiac failure, congestive cardiac failure, coronary artery occlusion, left ventricular dysfunction, myocardial infarction
Endocrine disorders: hypothyroidism
Gastrointestinal: Abdominal pain lower, abdominal pain upper, anal fistula, constipation, diverticular perforation, intestinal perforation, pancreatitis, acute pancreatitis, rectal hemorrhage, rectal perforation, stomatitis, upper gastrointestinal hemorrhage
General disorders and administration site conditions: Fatigue, malaise, peripheral edema, impaired wound healing
Hepatobiliary: Cholecystitis, cholecystitis acute, hepatic failure, hepatic function abnormal, hepatitis acute, hyperbilirubinemia, liver injury
Infections and infestations: Colonic abscess, perineal abscess, urinary tract infection, urosepsis
Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, ejection fraction increased, lipase increased, weight decreased
Metabolism and nutrition disorders: Hypocalcemia, hypokalemia, hypomagnesemia
Musculoskeletal and connective tissue disorders: Arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity
Neoplasms benign, malignant and unspecified: intracranial tumor hemorrhage, tumor hemorrhage
Nervous system: Cerebrovascular hemorrhage, cerebral infarction, cerebrovascular accident, dizziness, hemorrhage intracranial, headache, ischemic stroke, monoparesis, posterior reversible encephalopathy syndrome, subarachnoid hemorrhage, transient ischemic attack
Renal and urinary disorders: Hematuria, proteinuria, renal failure, renal impairment, renal tubular necrosis, nephrotic syndrome
Reproductive system and breast disorders: female genital tract fistula, vaginal hemorrhage
Respiratory, thoracic and mediastinal disorders: Epistaxis, hemoptysis, pulmonary hemorrhage, pneumothorax
Vascular: Arterial hemorrhage, aortic dissection

15.18 **Drug procurement:** Investigational lenvatinib is provided free of charge to patients by Eisai. Each participating ACCRU membership will order a starter supply of lenvatinib from Eisai.

E-mail the Lenvatinib Drug Order Request Form (found on the ACCRU web

site) to the following:

[redacted]

Include amount of drug needed and date your site must receive drug.
NOTE: drug shipments will take 3-4 days from receipt of drug order. No drug shipments are done on weekends or holidays.

Each participating ACCRU treating location will be responsible for monitoring the supply of lenvatinib and will use the drug ordering instructions above to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 **Nursing guidelines**

15.191 Hypertension is very common with agent. Monitor BP as per protocol and report BP elevations to the study team.

15.192 Diarrhea is common. This may be increased in patients who are undergoing simultaneous treatment with immunotherapy agents. Instruct patients to report any diarrhea immediately and treat symptomatically per protocol instructions.

15.193 Other GI side effects can occur, including decreased appetite, weight loss, and nausea/vomiting. Manage patients symptomatically and monitor for effectiveness.

15.194 Patients may experience fatigue. Instruct patients in energy conserving lifestyle.

15.195 Dermatologic related side effects have been seen, including: hand-foot syndrome, rash, and alopecia. Instruct patients to report these signs and symptoms to the study team immediately.

15.196 Patients may experience increased risk of bleeding. Instruct patients to report any unusual bruising or bleeding to the study team. Patients should not undergo invasive procedures without first discussing with the study team.

15.197 Monitor for proteinuria per protocol.

15.198 Rarely agent may cause decreased LVEF. Instruct patients to report any peripheral edema, DOE, chest pain or significant fatigue to the study team.

15.199 Monitor LFT's and renal function. Report any elevations to the provider.

15.2 **Pembrolizumab (Keytruda®)**

Investigator brochure is available on the ACCRU web site.

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

15.22 **Formulation**: Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.23 **Preparation and storage**: Vials should be stored in the refrigerator at temperatures between 2-8°C (36-46ºF).

Drug concentrate is further diluted with normal saline (or 5% dextrose) in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non-PVC material. The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. The product can also be stored under refrigeration at 2°C to 8°C for no more than 96 hours from the time of dilution. If refrigerated, the diluted solution must be allowed to come to room temperature prior to administration. The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

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

15.25 **Pharmacokinetic information**:

a) Absorption –Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W regimen and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.

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

c) Excretion – CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life (t½) is estimated to be 22 days at steady state.

d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

There are no limited clinical studies on the subcutaneous formulation. Model-based analysis showed an estimated bioavailability of 64% (95% CI: 54% to 74%; variability, 128% CV). This is consistent with the reported bioavailability for other mAbs (range: 50% to 85%) given SC. Clearance was the same for the IV and SC formulations. The mean time to achieve maximum concentration (T_{max}) with pembrolizumab SC was

estimated to be 5.5 days (range: 3 days to 14 days).

15.26 **Potential Drug Interactions:** There are no known significant drug interactions.

15.27 **Known potential toxicities**:

Very common known potential toxicities, > 10%:
Gastrointestinal: diarrhea nausea
Skin and subcutaneous tissue disorders: rash, pruritus
General disorders and administration site conditions: fatigue

Common known potential toxicities, > 1% - 10%:
Blood and lymphatic system disorders: anemia
Immune system disorders: infusion related reaction
Endocrine disorders: Hypothyroidism, hyperthyroidism
Gastrointestinal disorders: colitis, vomiting, abdominal pain, constipation, dry mouth
Metabolism and nutrition disorders: decreased appetite
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, arthritis, pain in extremity
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential toxicities, ≥0.1% to <1%:
Cardiac disorders: myocarditis
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Eye disorders: uveitis, dry eye
Endocrine disorders: hypophysitis, adrenal insufficiency, thyroiditis
Gastrointestinal disorders: pancreatitis, dysphagia
Hepatobiliary disorders: hepatitis
Infusion related reactions
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Musculoskeletal and connective tissue disorders: tenosynovitis
Nervous system disorders: epilepsy, lethargy, peripheral neuropathy
Psychiatric disorders: insomnia
Renal and urinary disorders: nephritis, acute kidney injury
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule
Vascular disorders: hypertension
Investigations: blood bilirubin increased, amylase increased, hypercalcemia
Respiratory: aspiration pneumonia

Rare known potential toxicities, <0.1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic purpura,

hemolytic anemia
Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum

The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide and dexamethasone, had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide. The benefit-risk profile is unfavorable for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment-naive multiple myeloma.

15.28 Drug procurement: Investigational pembrolizumab is provided free of charge to patients by Merck. Each participating ACCRU membership will order a starter supply of pembrolizumab from Merck.

E-mail the Pembrolizumab Drug Order Request Form (found on the ACCRU web site) to:

Merck, Inc.
[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of pembrolizumab and will use the Drug Order Request Form to order additional supplies as needed.

NOTE: in order to obtain a drug re-supply, Merck should be notified six months prior to study drug expiry.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29 **Nursing Guidelines:**

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

15.292 Diarrhea can be seen, however, it is less common than what is seen with anti-CTLA-4 agents. It can occasionally be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.293 Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.294 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.295 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any shortness of breath, dyspnea, cough, and/or chest pain to the study team immediately. Patients reporting these symptoms should have a pulse oximetry checked and consider immediate imaging per the treating physician.

15.296 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by the treating physician.

15.297 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.298 Fatigue is common and may or may not be associated with immune-related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.299a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.299b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and veno-occlusive disease, if they have previously been treated with pembrolizumab.

15.299c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.299d Autoimmune hematologic disorders including ITP and hemolytic

anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.299e Rare neurologic disorders including Guillain-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, paresthesia or numbness, tingling to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Study Design/Endpoints

16.11 Background/Overview**:** This novel study will be the first to assess pembrolizumab and lenvatinib combination therapy in advanced DTC (and in any cancer). There is an ongoing basket trial (KEYNOTE-028 (NCT02054806)) that has enrolled patients with advanced thyroid cancer to a single agent pembrolizumab (200 mg iv every 3 weeks) study. Preliminary data from the thyroid cohort in this trial was presented at the 2016 American Society for Clinical Oncology (Mehnert JM, et al, J Clin Oncol 34, 2016 (suppl; abstr 6091)). The study enrolled 22 patients with DTC, with a median duration of follow-up of 74 weeks (29-87 weeks). No patients achieved a CR (0%) and 2 patients had a PR (9.1%), with 12 having SD (54%), which is why we will not have a pembrolizumab-only arm in this study. Our study will be done for 2 different cohorts (Cohort 1: Lenvatinib-naïve patients; Cohort 2: progressed on Lenvatinib alone). Both cohorts will receive the same combination therapy. The primary endpoint is different for the 2 cohorts, as described below (16.12 and 16.14). This study will also assess many secondary endpoints as well, as explained in detail below (16.3). Finally, this study will also assess important correlative science endpoints (16.4).

16.12 Overview and Primary Endpoint for Cohort 1**:** The complete response (CR) rate for lenvatinib alone was around 2%. The CR for patients with advanced DTC treated with pembrolizumab is 0% (see Section 16.11). A CR rate of around 15% would be clinically significant and worthy of further study. The primary endpoint for Cohort 1 is this CR rate (per RECIST 1.1 criteria). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be considered evaluable for the primary endpoint. A patient that has a CR (Cohort 1) is considered a treatment "success". The following one-stage binomial design (see below) requires 25 evaluable patients, and simultaneously discriminates between CR rates of 2% vs. 15%.

16.13 Decision Rules for Cohort 1:

16.131 Final Analysis Decision Rule**:** Enroll 25 total evaluable patients. If at least 2 patients have a success (at least 8%) among the 25 evaluable patients, this combination therapy would be considered worthy of further testing in this disease. If 0 or 1 patients have a success, this combination therapy will be considered negative and no further study would be warranted.

16.132 Power and Significance Level: This design has 91% power to detect a

true success rate of 15%, with a significance level of 0.09 if the true success rate is 2%.

16.14 Overview and Primary Endpoint for Cohort 2: It is expected that the confirmed response rate is around 5% in this disease population. A confirmed response rate of around 25% would be clinically significant and worthy of further study. The primary endpoint for Cohort 2 is this confirmed response rate (per RECIST 1.1 criteria). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be considered evaluable for the primary endpoint. A confirmed tumor response is defined to be a CR or PR noted as the objective status on 2 consecutive evaluations at least 4 weeks apart. A patient that has a confirmed response (Cohort 2) is considered a treatment "success". The following 2-stage Simon Optimal MinMax design (see below) requires a maximum of 25 evaluable patients, and simultaneously discriminates between confirmed response rates of 5% vs. 25%.

16.15 Decision Rules for Cohort 2:

16.151 Final Analysis Decision Rule: Enroll 25 evaluable patients. If at least 4 patients have a success (at least 16%) among the 25 evaluable patients, this combination therapy would be considered worthy of further testing in this disease. If 3 or fewer patients have a success, this combination therapy will be considered negative and no further study would be warranted.

16.152 Stage 1 Decision Rule: After the first 15 patients entered into the trial become evaluable for the primary endpoint, a stage 1 analysis will be performed. If 1 or more patients have a success, the study will continue to full accrual. Otherwise, if 0 successes are observed, the study will be stopped early and the treatment will be considered ineffective in this patient population. Accrual will stop after we enroll the first 15 eligible patients to this cohort.

16.153 Power and Significance Level**:** This design has 90% power to detect a true success rate of 25%, with a significance level of 0.05 if the true success rate is 5%.

16.16 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.17 Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.2 Sample Size/Accrual Rate

16.21 Sample Size**:** A total of 25 evaluable Cohort 1 and 25 evaluable Cohort 2 patients will be accrued per study design (50 evaluable total), unless one or both cohorts of the study are permanently closed at the stage 1 analysis or undue

toxicity is observed. We anticipate accruing an additional 10 patients (5 Cohort 1, 5 Cohort 2) in order to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 60 patients for this trial (30 for each Cohort).

16.22 Accrual Time and Study Duration**:** We expect to accrue about 3 patients per month to this trial. Therefore, the accrual period for this Phase II study is expected to be about 20 months. We anticipate that the study will take approximately 3 years to complete. This allows a 6 month follow-up for the final patient enrolled, along with data entry, data clean-up, and analysis.

16.3 Analysis of Secondary Endpoints for both Cohorts.

This study will assess multiple secondary endpoints, including adverse events, progression-free survival (PFS) and overall survival (OS). All these analyses will be done for each cohort separately. In addition, all primary/secondary data will be summarized by descriptive factors as well (i.e. prior treatment, etc.).

16.31 Adverse Events: All patients that have initiated treatment will be considered evaluable for assessing adverse events. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine adverse event patterns. Only the grade 2+ adverse events will be assessed, regardless of relationship to the study treatment.

16.32 Progression-Free Survival (PFS): Defined as the time from registration to the first of either death due to any cause or progression. The distribution of PFS will be estimated using the method of Kaplan-Meier.

16.33 Overall Survival: Defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier. Special attention will be paid to any registered patient who dies early (i.e., within 60 days) of initiating their treatment. Circumstances surrounding such early deaths will be classified as being either due to malignant disease, toxicity, other causes, or of unknown reasons.

16.4 Laboratory Correlative Studies (all done by Cohort)**:** All analyses with respect to the translational component of this study are intended to be hypothesis-generating and descriptive in manner. Clinical data (i.e. CR rates confirmed response rates, PFS, OS, etc.) will be correlated with tumor marker data of interest (CD8+, PD-L1, PD-L2, T cell functional capacity markers, anti-thyroglobulin antibody levels, tumor mutation status, and other markers). The Chi-Square (or Fisher's Exact test) will be used to assess the association of categorical clinical data with categorical biomarker data. Time-to-event clinical data (PFS, OS) will be correlated with biomarker data using Kaplan-Meier methodology and Cox regression models. Logistic regression models will also be used to predict binary clinical data with baseline biomarker data. Finally, graphical methods and descriptive statistics will be used to summarize the data as well. Two-sided p-values < 0.05 will be considered statistically significant.

16.5 Adverse Event Stopping Rule:

16.51 Monitoring: The principal investigator and the study statistician will review the study periodically (at least twice a year) to identify accrual, toxicity, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. We expect approximately 10% of patients to experience grade 4+ adverse events (at least possibly related to study medication). In this study, we will suspend accrual to allow for a full review of the data, if any of the following occur in each cohort separately:

- If at any time, 3 of the initial 10 patients (or 30% of all patients when accrual is greater than 10) have experienced any grade 4 adverse event (at least possibly related to the study medication).

- If at any time, 1 of the initial 10 patients (or 10% of all patients when accrual is greater than 10) have experienced any grade 5 adverse event (at least possibly related to the study medication).

16.6 Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 3 patients per month, it is expected that the study will take around 20 months to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 5 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

16.7 Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting):

The primary endpoint is the complete response (CR) rate for Cohort 1 and the confirmed response rate for Cohort 2. The final analysis is expected to take place around 36 months after the study begins, so we expect the primary endpoint completion time to be around 36 months after study activation.

16.8 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Based on prior studies involving similar disease sites, we expect about 10% of patients will be classified as minorities by race and about 50% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	3	6
Not Hispanic or Latino	27	27	54
Ethnic Category: Total of all subjects	30	30	60
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	0	1	1
Black or African American	2	1	3
Native Hawaiian or other Pacific Islander	0	0	0
White	27	27	54
Racial Category: Total of all subjects	30	30	60

Ethnic Categories:

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

Not Hispanic or Latino

Racial Categories:

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

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

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

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

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

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission
NOTE: Patients must have consented to submission of the optional tissue(s) listed in the following table.

NOTE: Please refer to study specific Laboratory Manual.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background / methodology section)**	**Where to find specific details for biospecimen submission**	**Storage/Shipping conditions†**
Formalin-fixed paraffin-embedded (FFPE) primary tumor tissue blocks (**blocks preferred**, OR 30 four-micron unstained slides; Cohorts 1 and 2)	Mandatory	≤60 days after registration	Correlative studies (Section 2.31-2.33)	Section 17.3	Room temperature / Standard shipping
Formalin-fixed paraffin-embedded (FFPE) involved lymph node tissue blocks (**blocks preferred**, OR 30 four-micron unstained slides; Cohorts 1 and 2)	Mandatory (if available)	≤60 days after registration	Correlative studies (Section 2.31-2.33)	Section 17.3	Room temperature / Standard shipping
Formalin-fixed paraffin-embedded (FFPE) tissue blocks from biopsy of metastatic or locoregional tumor recurrence (Cohort 1)	Optional*	≤60 days after registration	Correlative studies (Sections 2.31-2.33 and 2.37-2.38)	Section 17.3	Room temperature / Standard shipping
RNA*later*®-preserved tissue biopsy from metastatic or locoregional tumor recurrence (Cohort 1)	Optional*	≤60 days after registration	Correlative studies (Section 2.37-2.38)	Section 17.3	Incubate the specimens in the RNA*later*® reagent at 4°C overnight and ship on ice. For long-term storage, transfer to -20°C and ship on dry ice

* Collection of this tissue is optional for research purposes. If a patient is not willing to undergo this procedure, it does not cause the patient to be ineligible; however, collection of this tissue is **strongly encouraged** (anticipate collecting samples from 20 of 30 patients in Cohort 1).
† See separate lab manual for detailed instructions.

17.2 Paraffin Embedded Tissue Blocks/Slides and Frozen Biopsy Samples

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from the original surgery (Cohorts 1 and 2). In addition, if available, submit one FFPE block containing tumor-involved lymph node. Preferably, chose a lymph node with gross tumor involvement. An H&E slide will be generated from all FFPE samples at the lead study site, which is responsible for correlative studies, to permit quality assessment of each tissue block. Once the QA is completed, and the necessary slides are cut, the tissue block will be returned. If tissue blocks cannot be released, prepare 30 slides for each tissue using the provided slides in the kit for each patient (See Laboratory Manual). Slides should not be baked since these tissues will be used for molecular studies. Slides should be shipped with 24 hours of tissue cutting.

17.22 A core biopsy will be performed after the patient is registered onto the study, but prior to the start of treatment from 20 patients in Cohort 1(see separate lab manual). Four passes will be obtained from tumor tissue in, but not limited to the neck, chest abdomen, pelvis, bone or extremities. The first two passes will be formalin fixed and paraffin embedded (FFPE). The second two passes will be preserved in RNA*later*® for future molecular analysis. An H&E slide will be generated from all samples at the University of Colorado, responsible for correlative studies, to permit quality assessment of the biopsies. (See Laboratory Manual)

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

- Paraffin embedded tissue blocks preferred (OR 30 four-micron unstained slides from primary tumor and involved lymph node).
- Specimen Submission: Tissue form
- Surgical Pathology Report
- Operative Report *(optional)*

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

17.24 The block/slides must be appropriately packed and shipped to prevent damage (see Appendix IV).

17.25 Tissue specimens must be shipped ≤**60** days after registration.

17.26 Verify that the appropriate sections of the Archival FFPE Tissue Submission Form and/or Biopsy Specimen Acquisition Tracking Form are completed and filled in correctly. (These forms are located on the ACCRU web site in the "Manuals & Forms" folder.)

17.3 Study Methodology and Storage Information

17.31 Submitted tissue samples will be analyzed as detailed in Section 2.3. DNA extraction and storage of DNA for future pharmacogenetic assays (e.g., for genetic polymorphisms such as BRAFV600E, NRAS, HRAS, KRAS, mutation burden, etc., that may correlate with efficacy and tolerability. DNA will be isolated from 30 FFPE primary tumor samples and 20 core biopsy frozen samples from progressive tumors (Cohort 1). To broadly investigate mechanisms of response and resistance to combination therapy, we plan to generate gene expression profiles from the frozen biopsies (n=20) for analysis by RNA-Seq. Total RNA will be isolated with the RNeasy kit (Qiagen) and 500ng of RNA will be submitted to our Genomics and Microarray core facility for mRNA-seq library construction (TruSeq Stranded mRNA Library Kit, Illumina). We aim to collect at least 20 pre-treatment biopsies, depending upon tumor accessibility and patient consent. In parallel, we will also analyze the 30 FFPE primary tumor samples by RNA-Seq[51]. RNA will be generated from FFPE tissue sections (Qiagen FFPE All-Prep kit) and 100ng will be submitted for library construction (TruSeq Stranded RNA Access mRNA Library Kit, Illumina). We plan to sequence 60-80 million 1x125bp (FFPE) or 2x125bp (frozen) reads per sample. DNA and RNA will be analyzed for mutations using whole-exome sequencing technology in the University of Colorado Cancer Center Gene Expression Core facility led by [redacted] Remaining DNA and RNA will be stored frozen at -80ºC at the University of Colorado, according to patient consent information (see Section 6.12) until specific analyses are identified. As protocols are developed, they will be presented for ACCRU, ITOG, and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.

17.32 At the completion of the study, any unused/remaining material will be stored in the University of Colorado Anschutz Medical Campus for future research according to the patient consent permission (see Section 6.15). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for ACCRU, ITOG and IRB review and approval.

17.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

17.5 Shipment of specimens and accompanying materials: Please refer to the Laboratory Manual.

18.0 Records and Data Collection Procedures

Access the RAVE system through the iMedidata portal at [redacted] All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Surgery	
On-Study: Prior Radioactive Iodine (RAI) Therapy	
On-Study: Prior Radiation	
On-Study: Prior VEGFR-Targeted Therapy (Cohort 2 Only)	
Adverse Event - Baseline	
Endocrine Laboratory Tests and Results: Baseline	
Concomitant Medications: Baseline	
RECIST Measurements: Baseline	
Supporting Documentation: Baseline (Op & Path reports - see Section 17)[1]	
Specimen Submission: Blood (Baseline – Cohort 1 Only (see Section 14))	
Specimen Submission: Blood (Baseline – Cohorts 1 & 2 (see Section 14))	
Patient Status: Baseline	
Specimen Submission: Tissue (Baseline, Cohort 1 Only – Optional (see Section 17))	≤60 days after registration
Specimen Submission: Tissue (Baseline, Cohorts 1 and 2 – (see Section 17))	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
ACCRU Deviation Form[2]	Submit only if applicable during ***all*** **phases** of the study (initial, active and observation)

1. Upload Op and Path Reports via the Supporting Documentation: Baseline form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. All participating ACCRU member sites must submit deviations using the ACCRU Deviation Form in the forms packet.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Treatment (Intervention)	X[1]	X[1]	
Treatment (Intervention): Dose Modifications, Omissions and Delays	X[2]		
Patient Status: Treatment (Intervention)	X	X	
Patient Status: Clinical Follow-up/Observation			X[3]
Adverse Events: Solicited	X	X	X
Adverse Events: Other	X	X	X
RECIST Measurements	X[4]	X[4]	X[4]
Supporting Documentation	X[4]	X[4]	X[4]
Endocrine Laboratory Tests and Results	X		
Concomitant Medications	X	X	X
Specimen Submission: Blood (Cohort 1 only)	X (see section 14.0)		
Specimen Submission: Blood (Cohorts 1 and 2)	X (see section 14.0)		
Consent Withdrawal (choose appropriate form)2 • Consent Withdrawal: Specimens Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up	X	X	X
Off Treatment		X	
ACCRU Deviation Form[2]	X[2]	X[2]	X[2]

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Submit only if applicable.
3. Complete at each evaluation during Observation (see Section 4.0).
4. Upload a copy of documentation of progression in RAVE on the Supporting Documentation Form.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]			
	At PD	After PD q. 6 mos.	Death	New Primary
Patient Status: Survival and Disease Status Follow-up/Event Monitoring	X	X	X	At each occurrence
Adverse Events: Late	X	X		
Notice of New Primary				X
Consent Withdrawal • Consent Withdrawal: Specimens Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up	X[2]	X[2]	X[2]	X[3]
Lost to Follow-up	X[2]	X[2]	X[2]	
ACCRU Deviation Form[2]	X[2]	X[2]	X[2]	

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. Submit only if applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Eisai will provide investigational lenvatinib free of charge to patients participating in this study.

19.3 Merck will provide investigational pembrolizumab free of charge to patients participating in this study.

19.4 Blood pressure monitors will be provided for patients who do not already have a blood pressure monitor.

19.41 Sites may order blood pressure monitors by submitting the Blood Pressure Monitor Ordering Contact Sheet to ACCRU Regulatory [redacted] ACCRU Regulatory will send the completed form to ITOG designated personnel who will then grant access to the blood pressure monitor ordering system. Once site personnel are notified that they have received access to the system, they may order blood pressure monitors via the following link: [redacted]

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ACCRU Informed Consent Template for Cancer Treatment Trials

(English Language)

***NOTES FOR LOCAL INVESTIGATORS:** **[NOTE: Retain this section and asterisk item below for ACCRU model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is [redacted]
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at [redacted] or call [redacted] to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Combination Targeted Therapy with Pembrolizumab and Lenvatinib in Progressive, Radioiodine-Refractory Differentiated Thyroid Cancers: A Phase II Study

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have differentiated thyroid cancer that has spread and has not responded to treatment with radioactive iodine.

Why is this research study being done?

The purpose of this research study is to determine any good and bad effects of using lenvatinib alone, or lenvatinib along with pembrolizumab. The study will allow researchers to see if there is any benefit to adding pembrolizumab to the standard treatment (lenvatinib).

How many people will take part in the research study?

This study has two study groups, and each group will have about 25 patients.

Group 1 includes people who have never received treatment with lenvatinib. These people will take 20 mg of lenvatinib by mouth, and receive 200 mg of pembrolizumab through an IV once every 21 days.

Group 2 includes people who are already taking lenvatinib but their cancer has continued to spread. These people will continue taking (or re-start) the lenvatinib at the same dose they had been taking, and will be given 200 mg of pembrolizumab through a needle in your arm (IV infusion) once every 21 days in addition to lenvatinib.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam, including pulse, blood pressure, height, weight and an assessment of how well you perform routine activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- A blood sample for research tests is required for this study. Before treatment starts, the research blood sample will be taken at the same time as the routine blood samples by drawing some blood from a vein. About 3 additional teaspoons of blood will be drawn.
- Urine test
- A pregnancy test done either by providing a urine sample or by taking a blood sample from a vein in your arm within 7 days of being registered on the study (if you are a woman of childbearing potential). Your study doctor will discuss these options with you.
- A measurement and evaluation of your tumor by MRI and/or CT scan.
- An echocardiogram and electrocardiogram to look at your heart and heart valves to see how well they are working.
- A check to see if any of the side effects that may be caused by the study drugs are already present.

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical history and physical exam, including pulse, blood pressure, height, weight and an assessment of how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Urine test.
- A MRI and/or CT scan to measure and evaluate your tumor, and to find out if your disease is progressing.
- An echocardiogram and electrocardiogram to look at your heart and heart valves to see how well they are working.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- A check to see if you are having any of the side effects that may be caused by the study drugs.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Urine test.
- An echocardiogram and electrocardiogram to look at your heart and heart valves to see how well they are working.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- A blood sample for research tests is required for this study. Before treatment starts, the research blood sample will be taken at the same time as the routine blood samples by drawing some blood from a vein. About 3 additional teaspoons of blood will be drawn.
- Mandatory tumor tissue submission: This study also includes research tests that will be performed on tumor tissue samples that you will provide. These samples should be tissues that were obtained from previous surgeries or biopsies; no additional tumor tissue will be taken from you during this study.
- A check to see if you are having any of the side effects that may be caused by the study drugs.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Urine test.
- An echocardiogram and electrocardiogram to look at your heart and heart valves to see how well they are working.
- **If you are in Group 1:** An additional ***optional*** biopsy of your current tumor tissue may be performed. The biopsies will be performed by specialists at your facility who are trained to do these biopsies. The specific procedure to be performed will depend on the site of your tumor. The specific details and risks of the specific procedures will be explained to you by the specialist who will perform the biopsy. The specialist will use an ultrasound or CT scan to help them take the biopsy. Before the sample is taken, you will be given some medicine to numb the area. A small cut will be made in your skin and the sample will be taken by pressing a hollow needle into your tumor. When we take the needle out, it will remove a small circle of tumor tissue called a "plug." A total of four "plugs" will be taken.

Some of the research tests done on the research blood and tissue samples are genetic tests. Because these genetic tests are not used for regular medical care, neither you nor your doctor will be told the results of the test(s). The test results will not be put in your medical record either.

There is more information about these research tests near the end of this form.

You will be asked to keep a daily record of when you take the study medication (Patient Medication Diary), and every day write down the day and time you take the medication. If you notice any side effects, you can include this information in the Comments section of the diary. You will be asked to bring the medication diary each time you see your doctor.

You will also be asked to check your blood pressure three times every week, and record it on the Blood Pressure Diary. If you do not already have a blood pressure monitor, one will be provided to you. You will be asked to bring the Blood Pressure Diary each time you see your doctor.

Study Calendar

You will take lenvatinib every day. Every 21 days you will go to your treating facility to receive pembrolizumab by IV. This 21-day period of time is called a cycle. The cycle will be repeated until your disease gets worse. The chart below shows what will happen to you during the entire 54-week treatment period (19 cycles).

The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day. Patients in both groups will do everything listed in the "What you do" column, unless otherwise specified.

Groups 1 and 2	
Day	**What you do**
Up to 30 days *before* starting study	• Medical history and physical exam, including pulse, blood pressure, height, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Mandatory research blood samples • Pregnancy test (if applicable) • Urine test • MRI and/or CT scan for tumor measurement • Echocardiogram or multigated acquisition (MUGA) scan • Electrocardiogram • **GROUP 1 ONLY: *Optional*** tumor biopsy.
Cycle 1, Day 1	• Medical history and physical exam, weight, and blood pressure. • Routine blood tests • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. This infusion will take approximately 25-40 minutes. (This can be done 3 days before or after the scheduled day if your treating facility is closed on the scheduled day). • Begin taking 20 mg of lenvatinib once each day. Lenvatinib is in capsule form and you will need to two 10-mg capsules, for a total of 20mg. The capsules should be taken with water at about the same time each day, and can be taken with or without food, and should be taken every day that you are in the study. • Each day, in the Patient Medication Diary, write down when you take the study medication and any side effects you notice. • Three times each week during treatment, check your blood pressure and record it on the Blood Pressure Diary.
Within 60 days *after* starting study	• Mandatory archival tissue collection. (NOTE: Receipt of archival tumor tissue is not required for study registration or initiation of therapy.)

Cycle 2, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 3, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Electrocardiogram • Routine blood tests • **GROUP 1 ONLY:** Mandatory research blood sample • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 4, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 5, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 6, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests

	• Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 7, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Medical history and physical exam, including blood pressure, weight and assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Mandatory research serum sample • Mandatory research blood sample • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 8, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 9, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Echocardiogram or multigated acquisition (MUGA) scan • Electrocardiogram • Routine blood tests • Urine test • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 10, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of

	pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 11, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 12, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 13, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Echocardiogram or multigated acquisition (MUGA) scan • Electrocardiogram • Routine blood tests • Urine test • Medical history and physical exam, including blood pressure, weight and assessment of how well you perform activities of daily livingA check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 14, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused

	by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 15, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 16, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 17, Day 1	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • Echocardiogram or multigated acquisition (MUGA) scan • Electrocardiogram • Routine blood tests • Urine test • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff
Cycle 18, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • Routine blood tests • Urine test • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab. • A check to see if you are having any of the side effects that may be caused by the study drugs. • Review your Patient Medication and Blood Pressure diaries with study staff

Cycle 19, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Group 1 ONLY: Mandatory research blood sample • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 20, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 21, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 22, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.

Cycle 23, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 24, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 25, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Echocardiogram or multigated acquisition (MUGA) scan • Electrocardiogram • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 26, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.

Cycle 27, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 28, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 29, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 30, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 31, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement

	• Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 32, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 33, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Echocardiogram or multigated acquisition (MUGA) scan • Electrocardiogram • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab
Cycle 34, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • Review your Patient Medication and Blood Pressure diaries with study staff • Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab.
Cycle 35, Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff

	• Go to your treating facility to receive the IV infusion of 200 mg of pembrolizumab
You will continue the schedule above until your disease gets worse or you stop treatment for any reason.	

When I am finished with treatment

When you finish treatment, you will need the following tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

Study Calendar Following Completion of Therapy

Day	What you do
Day 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • **GROUP 1 ONLY:** Mandatory research blood sample • Urine testMRI and/or CT scan for tumor measurement • Review your Patient Medication and Blood Pressure diaries with study staff
Every 12 weeks	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living • A check to see if you are having any of the side effects that may be caused by the study drugs. • Routine blood tests • Urine test • MRI and/or CT scan for tumor measurement, per treating physician as clinically indicated

How long will I be in the research study?

You will be asked to take the combination of lenvatinib and pembrolizumab until your disease gets worse, you choose to withdraw from the study, or your doctor indicates you should discontinue the study, for a maximum of 24 months (on treatment) . After you are finished

taking the combination of lenvatinib and pembrolizumab, the study doctor will ask you to visit the office for follow-up exams every 12 weeks unless and until your disease gets worse, for a maximum of up to5 years.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from taking the combination of lenvatinib and pembrolizumab can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the combination of lenvatinib and pembrolizumab. In some cases, side effects can be serious, long lasting, or may never go away.

There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Pembrolizumab include those which are:

Very common side effects (seen in more than 10% of people taking pembrolizumab):

- Feeling tired
- Itching of the skin
- Rash
- Frequent or excessive bowel movements or diarrhea
- Fever
- Shortness of breath
- Decreased appetite
- Cough
- Nausea and vomiting
- Decreased in red blood cells that may result in patients feeling tired or short of breath
- Pain in a joint
- Headache
- Swelling of the legs

- Muscle weakness or lack of energy
- Bowel movements occurring less often than usual (Constipation)

Common side effects (seen in 1-10% of people taking pembrolizumab) include the following:

- Pain or cramping in a muscle or group of muscles
- Decreased release of thyroid hormone. Symptoms may include feeling tired, feeling cold easily, weight gain, or bowel movements occurring less often than usual
- Abnormal laboratory result of liver test by blood that occasionally indicates liver failure, may have yellowing of the skin or whites of the eyes, fatigue, or leg swelling
- Feeling cold or sick
- Loss of skin color
- Pain or uncomfortable feeling in the belly
- Bowel movements occurring less often than usual
- Momentary feeling of whole body warmth possibly along with sweating
- Sweating a lot while sleeping such that clothes and sheets are wet ("night sweats")
- Feeling dizzy or unsteady when walking or standing
- Weight loss
- Pain in the back, arms, or legs
- Swelling of the legs
- Decreased platelets that may cause you to bruise or bleed easily
- Dry eyes
- Blurred or changed vision
- Dry mouth
- Feeling of pain, pins & needles, or burning, usually in the fingers or toes
- Back pain
- Irritated or swollen lungs
- Change of blood cholesterol or triglyceride level
- Change of blood sugar or albumin level
- Change of blood electrolytes, e.g. sodium, potassium, or magnesium
- Loss of body fluid may feel tired, confused, have a dry mouth, or feel thirsty
- Lung infection
- Fluid around the lung
- Blood clot developed in lung
- Inflammation of the large intestine (colon) that may lead to frequent or excessive watery bowel movements

Serious Adverse Events (No event occurred in more than 2% of people taking pembrolizumab):

Please note that some of these events have been previously stated above, so some have occurred more frequently but with less severity. Serious adverse events seen in people taking pembrolizumab include the following:

- Trouble thinking clearly or easily confused
- Decreased white blood cells, red blood cells, and platelets which may cause fever, feeling cold, infections, shortness of breath, feeling tired, a tendency to bruise easily, or a tendency to bleed easily
- Increased release of thyroid hormone which may cause anxiety, irritability, or trouble sleeping, weakness, trembling, sweating, feeling uncomfortable in warm weather, fast or uneven heartbeats, feeling tired, weight loss, and frequent or excessive bowel movements.
- Infection throughout the body by a fungus or bacteria or others that may cause fever, feeling tired, feeling cold, and that does not respond to most antibiotics. **This is serious and can be life-threatening.**
- Inflammation of the lining around the heart which may cause sharp chest pain and/or fever.
- Inflammation of the pancreas. Symptoms may include abdominal pain that radiates to the back, swollen or tender abdomen, fever, nausea and/or vomiting.
- Inflammation of the muscles. Symptoms may include weakness or pain in the muscles.
- Inflammation of the kidneys causing them not to work as well, which may cause swelling of the legs and possibly a need for dialysis.
- Inflammation of the pituitary gland, which may cause headache, nausea, a sensation of the room spinning around you, changes in behavior, double vision, or weakness
- Irritation of body systems that may cause feeling sick to your stomach, high body temperature, chills, low blood pressure, increased heart rate, weakness, headache, rash, and/or difficulty breathing (Cytokine Release Syndrome).
- Change of blood pressure or body fluid level that may cause you to feel dizzy.
- Failure of liver or lung function that may cause yellowing of the skin or eyes, or difficulty breathing
- Damage of the peripheral nerves that may cause weakness
- Cancer of the skin
- Inflammation of the heart muscle which can cause shortness of breath or heart rhythm problems. May be serious and require hospitalization. (Immune-mediated myocarditis)
- Severe skin and digestive tract reaction that may include rash and sloughing or breakdown of tissue. This may manifest as various blisters, hives, and other lesions in various locations on the body including palms and soles, face and other extremities. This is serious and may be life threatening. [Stevens-Johnson Syndrome (SJS)] or Toxic Epidermal Necrolysis (TEN).
- Myasthenic Syndrome (causes muscle weakness)
- Guillain-Barre Syndrome (damage to the nervous system (causing numbness and/or paralysis))

- High blood calcium (can cause fatigue, weakness, confusion, kidney stones, kidney damage)

Other less common side effects have been reported. The study doctor or staff can discuss these with you.

There may be other side effects or risks that are not known at this time.

There is also a risk of death.

Risks and side effects related to Lenvatinib include those which are:

Likely *(events occurring greater than 20% of the time)*

- High blood pressure
- Diarrhea
- Decreased Appetite
- Weight loss
- Nausea
- Mouth sores
- Fatigue
- Headache
- Vomiting
- Loss of protein into the urine
- Bleeding
- Sensitivity and irritation/rash, palms and soles (potentially severe)
- Abdominal pain
- Voice changes
- Mouth pain
- Cough
- Arm and/or leg swelling (Edema)
- Pain in the joints, back, muscles and/or limbs (Myalgias/arthralgias)
- Nose bleeds
- Dry mouth
- Problems swallowing
- Lack of energy (Asthenia)

Less likely *(events occurring less than or equal to 20% of the time)*

- Skin Rash or growths
- Indigestion/heartburn (Gastrointestinal reflux, GERD)
- Hair loss (Alopecia)
- Change in taste sensation (Dysgeusia)
- Dizziness
- Low platelet count (blood cells responsible for blood clotting; thrombocytopenia)
- Low lymphocyte count (blood cells responsible for fighting some infections including fungal infections; lymphopenia)
- Anemia
- Sleep difficulties (Insomnia)
- Urinary tract infection
- Dehydration
- Shortness of breath (Dyspnea)
- Low blood pressure (Hypotension)

- Low blood level of potassium (Hypokalemia)
- Low blood level of sodium (Hyponatremia)
- Low blood level calcium (Hypocalcemia)
- Low blood level of proteins (Hypoproteinemia)
- Low blood level of magnesium (Hypomagnesemia)
- Altered heart electrical conduction (ECG changes)
- Increased liver tests/worsened liver function (Hepatitis)
- Worsening kidney function
- Low thyroid function/altered thyroid function tests
- Decreased heart pumping function (Decreased cardiac ejection fraction)
- High cholesterol (hyperlipidemia/cholesterolemia)
- Increased passing gas (Flatulence)
- Fever (pyrexia)
- Gall bladder inflammation (Cholecystitis)
- Upper respiratory or lung infection (Bronchitis, Pneumonia)
- Pain or bleeding at sites of cancer
- Headache
- Fainting (Syncope)
- Depression/altered mental status/anxiety (may be severe)
- Muscle spasms
- Itching
- Tongue pain
- High blood sugar (Hyperglycemia)

Rare but serious risks *(events occurring less than 2-3% of the time)*

- Stroke (Cerebrovascular accident)
- Weakness of one limb
- Seizure (Epilepsy)
- Temporary brain inflammation (Reversible posterior leukoencephalopathy)
- Chest pain from heart blockage (Angina)
- Heart attack (myocardial infarction)
- Heart failure (Congestive heart failure)
- Irregular heart rhythm (Atrial fibrillation, tachycardia)
- Blood clots in veins and/or in lungs (Deep venous thrombosis or/and pulmonary embolism)
- Bleeding (in bowel movements/rectal bleeding, urine, coughing up blood)
- Inflammation of the pancreas (Pancreatitis)
- Liver inflammation or failure (Hepatitis)
- Kidney failure (Renal failure)
- Infection pocket in groin/around anus (Abscess)
- Injury to spleen (splenic infarction)
- Fluid build-up in abdomen (Ascites)
- Fluid build-up around the lungs (Pleural effusions)
- Yellowing of the skin/jaundice (Hyperbilirubinemia)
- Intestinal break/leakage (perforation)
- Infection in the appendix (Appendicitis)
- Inflammation of the gall bladder (Cholecystitis)
- Skin infection (Cellulitis)
- Infection in bloodstream (Sepsis)
- Suicidal thoughts
- Breathing failure (Respiratory failure)
- Abnormal connections between organs (Fistulas, including between bowel and skin,

bladder and/or vagina)
- Air leakage around lungs (Pneumothorax)
- Intestinal blockage (Bowel obstruction)

As with any medication, allergic reactions are a possibility.

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

Group 1 only – if you agree to the optional tumor biopsy: Risks and side effects of the needle biopsy of tumor tissue are:

- Small chance of infection at the needle site
- Bleeding or bruising at the needle site or along the needle path to the tumor
- Small scar at the needle site
- Small chance of an allergic reaction to the numbing medicine
- For biopsies of lung tumors and some liver and kidney tumors, there is a small risk of a pneumothorax. A pneumothorax is introduction of air around the lung that can partially collapse the lung and make breathing difficult. Some patients with pneumothorax will need a chest tube, which is a plastic tube inserted into the chest to remove the air and allow the lung to expand again. This requires hospitalization usually for 2-5 days.
- The specialist performing the biopsy will perform a full consent at the time of your procedure

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

[Note to Local Investigators: Include a statement about possible sterility when appropriate. For example, "Some of the drugs used in the study may make you unable to have children in the future." If appropriate include a statement that pregnancy testing may be required.]

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope the combination of lenvatinib and pembrolizumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the combination of lenvatinib and pembrolizumab as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study, if one is available
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Government agencies, like the Food and Drug Administration (FDA), Office for Human Research Protections or other federal, state, or international regulatory agencies involved in keeping research safe for people;
- Local Institutional Review Boards;
- Pharmaceutical companies supporting the study (Merck and Eisai);
- Your insurance company (if charges are billed to insurance);
- International Thyroid Oncology Group (ITOG);
- Academic and Community Cancer Research United (ACCRU) Coordinating Center.

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You **WILL** have to pay for:

- All doctor's visits, including physical exams, and medical histories
- Review of your tumor tissue (Pathology review)
- Routine blood test to check your health
- Pregnancy test
- Urine test
- All standard imaging done while on the study (CT scans, MRI scans, echocardiograms, electrocardiograms, etc.)

You will **NOT** have to pay for:

- Lenvatinib or pembrolizumab. Merck is supplying pembrolizumab, and Eisai is supplying lenvatinib at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you lenvatinib and pembrolizumab. NOTE: if you should need to take the study agents much longer than usual, the stock of free study agents could run out. If this happens, your study doctor will discuss with you how to get more of the study agents from the manufacturer, and you may be asked to pay for them.
- Mandatory serum samples for research purposes
- Mandatory blood samples for research purposes
- Costs to submit mandatory tumor tissue for research purposes (this is tissue from your original tumor obtained from previous surgery)
- Optional tissue biopsy for research purposes
- Blood pressure monitor if you do not already have one as a result of current or prior therapy with lenvatinib.

You will not be paid for taking part in this study.
For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted] You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call [redacted] and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*
[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

PLEASE NOTE: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About Using Biological Samples for Research

This study also has optional laboratory tests that will be performed to study small samples of tissue from patients in Group 1. Should you choose to participate in this portion of the study, you will have a biopsy (or surgery) so your doctor can remove some body tissue to do some additional tests.

The tissue will be sent to the Division of Endocrinology, Metabolism, and Diabetes Research Unit at the University of Colorado, School of Medicine where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not

be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

You can take part in the treatment portion of this study without taking part in these research laboratory tests.

Please read the following statements and mark your choice:

1. **Group 1 patients only:** I agree to provide tissue to University of Colorado, School of Medicine laboratories associated with ACCRU/ITOG for research testing planned as part of this study.

   ☐ Yes ☐ No Please initial here: _____ Date: _____

We would also like to keep some of the tissue and blood that is leftover for future research. If you agree, this leftover tissue and blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the online booklet called "Providing Your Tissue for Research: What You Need To Know," to learn more about tissue research:
[redacted]

Your leftover tissue and blood may be helpful for research whether you do or do not have cancer. The research that may be done with your leftover tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your leftover tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the leftover tissue and/or blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your leftover tissue and/or blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and/or blood; then any tissue and/or blood that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While ACCRU/ITOG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and/or blood are used for genetic research (about diseases that are passed on in families). Even if your tissue and/or blood is used for this kind of research, the results will not be put in your health records.

Your leftover tissue and/or blood will be used only for research and will not be sold. The research done with your leftover tissue and/or blood may help to develop new products in the future.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My tissue sample(s) may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. My blood sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

4. My blood sample(s) may be kept for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.

ACCRU/ITOG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of ACCRU/ITOG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call ACCRU and ask for samples for their studies. ACCRU looks at the way that these studies will be done, and decides if any of the samples can be used. ACCRU sends the samples and some information about you to the researcher. ACCRU will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside ACCRU use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at ACCRU. Then ACCRU will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

I permit ACCRU/ITOG to give my tissue sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

I permit ACCRU/ITOG to give my tissue sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You may also visit the NCI Web site at [redacted]

- For NCI's clinical trials information, go to: [redacted]
- For NCI's general information about cancer, go to [redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

PATIENT'S BLOOD PRESSURE DIARY

Today's date _____

Patient Name _____ (*initials acceptable)* Study Number _____

INSTRUCTIONS TO THE PATIENT:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heartbeat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, 110/85).
2. Record the date, then record your blood pressure. Your blood pressure should be monitored and recorded at least three times every week during therapy (for example, Mondays, Wednesdays, and Fridays). You should take your blood pressure after you have been sitting at rest for 5 minutes. Do not cross your legs.
3. Normal blood pressure is usually about 120/80 mmHg. If your systolic pressure is greater than 160 and/or your diastolic blood pressure is greater than 100 please rest for 15 - 20 minutes and then recheck your blood pressure. After resting, if your systolic pressure is still greater than 160 and/or your diastolic blood pressure is still greater than 100, please contact your doctor's office at _____ for instructions.
4. Please bring this form to every clinic visit or appointment.

Date	Blood Pressure Reading	Other readings (include time of day)	Date	Blood Pressure Reading	Other readings (include time of day)
	/			/	
	/			/	
	/			/	
	/			/	
	/			/	
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	/			/	

Patient's Signature: _____ Date: _____

This Section to be Completed by Study Staff Only

_____ _____

Date of this clinic visit Physician/Nurse/Data Manager's Signature

PATIENT MEDICATION DIARY
(Lenvatinib)

Today's date _____
Patient Name _____ (*initials acceptable)* Study Number _____

INSTRUCTIONS TO THE PATIENT:

1. You will take two 10-mg capsules each day , for a total dose of 20 mg). It is recommended that you take the capsules with water at about the same time each day, with or without food.
2. *Every day,* in the table below, write the date, time you took the lenvatinib, and the amount (e.g., 20 mg).
3. If you miss a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.. Place a "**0**" under **"Dose"**, but remember to take your prescribed dose at the next regularly scheduled time. NOTE: If you vomit after taking the daily dose of Lenvatinib, DO NOT repeat dosing. Resume dosing on the morning of the next day. Remember to write a comment on your diary if this happens.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Contact your physician and study coordinator any time you go into the hospital. Your study doctor can advise if you should stop taking lenvatinib or continue it.
6. Please bring your pill bottle, including any unused medication, and this form to your study doctor when you go for your next appointment.
7. Store your study drug at normal room temperature and keep out of the reach of children and pets.

Day	Date & Time	Dose	Comments
1			
2			
3			
4			
5			
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16			
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18			
19			
20			
21			

Patient's Signature: _____ Date: _____

This Section to be Completed by Study Staff Only

1. Patient's planned daily dose: _____
2. Total number of pills taken this month: _____
3. Number of pills returned: _____ Study Coordinator Signature: _____