Phase Ib/II Study of Pembrolizumab with Lanreotide Depot for Gastroenteropancreatic Neuroendocrine Tumors (PLANET)

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Protocol

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A National Cancer Institute-designated Comprehensive Cancer Center

Phase Ib/II Study of Pembrolizumab with Lanreotide Depot for Gastroenteropancreatic Neuroendocrine Tumors

(PLANET)

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PROTOCOL SYNPOSIS

Title

Phase Ib/II Study of **P**embrolizumab with **La**nreotide Depot for Gastroenteropancreatic **N**euro**e**ndocrine **T**umors (PLANET)

Objectives

The primary objective is:

1. To evaluate the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to pembrolizumab in combination with lanreotide depot in subjects with progressive, advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

The secondary objectives are:

1. To assess the safety of pembrolizumab in combination with lanreotide depot in subjects with GEP-NETs.
2. To assess progression free survival (PFS) of pembrolizumab in combination with lanreotide depot in subjects with GEP-NETs.
3. To assess the overall survival (OS) of pembrolizumab in combination with lanreotide depot in subjects with GEP-NETs.
4. To evaluate the ORR by Immune-Related Response Criteria (irRC) to pembrolizumab in combination with lanreotide depot in subjects with progressive, advanced or metastatic GEP-NETs.

The exploratory objectives are:

1. To characterize changes in circulating immune cells in subjects with GEP-NETs treated with pembrolizumab in combination with lanreotide depot.
2. To determine whether safety and efficacy parameters (ORR, PFS, OS) correlate with PD-L1 expression within the tumor in pre-treatment specimens.
3. To explore the correlation between blood-based biomarkers and clinical outcomes.

Patient Population

Patients must have a non-resectable, recurrent, or metastatic well or moderately differentiated gastroenteropancreatic neuroendocrine tumor (GEP-NETs) with at least one measurable lesion of the disease on imaging and evidence of radiological tumor progression within the last 12 months.

Study Design

The study will be conducted in two stages: 1) Safety Run-In and 2) Expanded Cohort.

Safety Run-In: The first stage will include a safety run-in of 6 patients treated with pembrolizumab 200 mg intravenous (IV) every 3 weeks and lanreotide depot 90mg subcutaneous (SQ) every 3 weeks. Up to 6 patients at the Duke Cancer Institute will be accrued at the starting dose level. If one or less subject meets treatment-related

discontinuation criteria (as specified in the protocol) during Cycle 1, then the study will proceed to the second stage, Expanded Cohort. If more than one subject meets treatment-related discontinuation criteria (as specified in the protocol) during Cycle 1, then the study will be redesigned to include alternative dose levels.

Expanded Cohort: The second stage will include an expanded cohort of up to 20 patients enrolled at the Duke Cancer Institute and select Duke Cancer Network sites. Patients will be treated with pembrolizumab 200mg IV every 3 weeks and lanreotide depot 90mg SQ every 3 weeks as determined by the Safety Run-In Cohort.

Number of Subjects

In the Safety Run-In Cohort, there will be up to 6 evaluable subjects.

In the Expanded Cohort, there will be up to 20 evaluable subjects.

Estimated Length of Study Participation

Patients may continue to receive study drug regimen until they experience unacceptable treatment-related toxicity, disease progression, or once they have been treated for 2 years (or received 35 administrations of pembrolizumab) at which they will revert to commercial use of lanreotide depot alone without pembrolizumab.

Patients will be followed for survival for up to 48 weeks after the last subject has finished study drug regimen.

Study Drug Regimen

Cycle length is 21 days.

Pembrolizumab is supplied as powder for solution for infusion in 50mg per vial, powder for solution for infusion. The dose and schedule is 200mg IV on Day 1 of each cycle.

Lanreotide depot is supplied as 90 mg/0.3 mL single use prefilled syringes for injection. The dose and schedule is 90mg SQ on Day 1 of each cycle.

Study Assessments

Toxicity and safety assessments will be monitored on an ongoing basis (refer to Study Calendar). Assessments include vital signs, ECOG performance status, medical history, physical examination, review of adverse events and laboratory studies. Toxicity management and supportive care will be provided as clinically indicated to ensure optimal patient care.

Adverse event seriousness, grade, and relationship to study drug will be assessed by the Investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Tumor Assessments

Disease response will be assessed using both RECIST 1.1 and Immune-Related Response Criteria (irRC). Patients will undergo radiographic imaging every 4 cycles (ie.12 weeks) after the start of the study drug regimen.

Correlative Studies

Tumor tissue will be assessed for level of PD-1 (infiltrating T cells) and PD-L1 expression (tumor and infiltrating immune cells). Blood will be collected at specified time points (see Study Calendar) for circulating immune cells and protein multiplex arrays.

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1.0 INTRODUCTION

1.1 Background

Neuroendocrine tumors of the gastrointestinal (GI) tract and pancreas (GEP-NETs) are generally indolent tumors which are nonetheless lethal once they become metastatic (1,2). Treatments include surgery, ablative procedures including embolization for liver metastases, systemic therapies targeting mammalian target of rapamycin (mTOR) or the vascular endothelial growth factor (VEGF) receptors (3). For patients with symptoms associated with hormone hypersecretion in neuroendocrine tumors, somatostatin analogues (SSA) are generally used (4). Furthermore, recent studies suggest somatostatin analogues also have antitumor effects (5,6). For example, the CLARINET study demonstrated that first-line treatment with Lanreotide Autogel/Depot, a somatostatin analogue (SSA), significantly prolonged progression free survival (PFS) among patients with metastatic nonfunctioning, somatostatin receptor-positive enteropancreatic NETs of grade 1 or 2 (Ki-67 <10%) (6). However, patients ultimately have progression of disease, indicating the need for additional therapies that could be combined. Because immune cells have been demonstrated to infiltrate neuroendocrine tumors (7), one class of therapies that may be potential partners for lanreotide includes immunotherapies. Indeed, while the anti-proliferative effects are likely direct effects mediated through the somatostatin receptors, somatostatin analogues such as lanreotide also may have immunomodulatory effects as somatostatin receptors are present on human lymphocytes and monocytes (8). Interferon alpha also has been used to treat neuroendocrine tumors with anti-tumor benefit similar to that of the somatostatin analogues (9). It is not known whether interferon is acting through immune mechanisms or other anti-proliferative or anti-angiogenic mechanisms. Interferon and lanreotide have been tested as a combination which was tolerable, but did not yield additive benefits; however, because the immunomodulatory molecules PD-1 and PD-L1 have been identified within neuroendocrine carcinomas (10), we hypothesize that a combination of an immunotherapy (anti-PD-1 antibody) with a different mechanism of action when combined with lanreotide will have greater anti-tumor activity.

1.2 Study Drugs

1.2.1 Pembrolizumab

The programmed cell death 1 (PD-1) pathway represents a major immune control switch, which may be engaged by tumor cells to overcome active T-cell immune surveillance. Pembrolizumab (KEYTRUDA®, MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligants, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Merck, Sharp & Dohme Corporation, a subsidiary of Merck & Co., Inc. (Merck), is studying pembrolizumab for various oncology indications. Overall, as of 03-Mar-2016, 16,496 patients have been treated in the pembrolizumab development program, of which approximately 9833 patients have been exposed to pembrolizumab in Merck sponsored clinical trials (approximately 6713 subjects received pembrolizumab monotherapy, approximately 876 subjects received pembrolizumab in combination with one or more other chemotherapy or biologic agents, and approximately 2244 subjects received comparator treatment alone). As of the various data cutoff dates for the KEYTRUDA® Investigator Brochure (IB) Version 11 dated 01-Sep-2016, pembrolizumab monotherapy and combination therapy

have been administered to subjects with hematologic malignancies and solid tumors, in a total of 48 ongoing, Phase 1, 2, and 3 clinical trials sponsored by Merck.

On 04-Sep-2014 the United States (US) Food and Drug Administration (FDA) granted accelerated approval to KEYTRUDA® for treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. KEYTRUDA® is the first approved drug that blocks PD-1. KEYTRUDA® is intended for use following treatment with ipilumumab (IPI), a type of immunotherapy. For melanoma patients whose tumors express a gene mutation called BRAF V600, KEYTRUDA® is intended for use after treatment with IPI and a BRAF inhibitor, a therapy that blocks activity of BRAF gene mutations. The recommended dose of KEYTRUDA® is 2 mg/kg administered as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W).

On 22-Jul-2015 the European Commission (EC) approved KEYTRUDA® for the treatment of advanced (unresectable or metastatic) melanoma in adults. The EC approval of KEYTRUDA® was based on data from 3 clinical studies (KEYNOTE [KN]001, KN002, and KN006) conducted in more than 1,500 first-line and previously-treated patients with advanced melanoma. KEYTRUDA® received EC regulatory approval based on Phase 3 data that showed it as the first and only anti-PD-1 therapy to provide a statistically superior survival benefit as a monotherapy compared to IPI, the current standard of care for advanced melanoma. This approval allowed marketing of KEYTRUDA® in all 28 EU member states at the approved dose of 2 mg/kg Q3W. With the EC decision, KEYTRUDA® is now approved in more than 35 countries for the treatment of advanced melanoma.

On 02-Oct-2015 the US FDA granted accelerated approval for KEYTRUDA® to treat patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments ans with tumors that express a protein called PD-L1. KEYTRUDA® is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors. The FDA-approved dose of KEYTRUDA® is 2 mg/kg Q3W.

On 18-Dec-2015, the US FDA expanded the label to include the approval of KEYTRUDA® for the treatment of patients with unresectable or metastatic melanoma. This expansion now includes the initial treatment of patients with unresectable or metastatic melanoma with pembrolizumab. The FDA-approved dose of KEYTRUDA® is 2 mg/kg Q3W.

On 02-Aug-2016 the EC approved KEYTRUDA® for patients with locally advanced or metastatic NSCLC, at a dose of 2 mg/kg Q3W, in patients whose tumors express PD-L1 and who have received at least 1 prior chemotherapy regimen. Patients with EGFR or ALK positive tumor mutations should also have received approved therapy for these mutations prior to receiving KEYTRUDA®. The EC approval allows marketing of KEYTRUDA® in all 28 EU member states. The approval is based on findings from KN010, a pivotal study which showed KEYTRUDA® significantly improved overall survival (OS) compared to standard of care chemotherapy.

On 05-Aug-2016 the US FDA approved KEYTRUDA®, at a fixed dose of 200 mg Q3W, for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. Under the FDA's accelerated approval regulations, this indication for KEYTRUDA® is approved based on tumor response rate and durability of response. For HNSCC patients, PD-L1 testing is not needed prior to use of KEYTRUDA®. The FDA-approved dose of KEYTRUDA® is 200 mg Q3W.

Merck is advancing a broad and fast-growing clinical development program for KEYTRUDA® both as a monotherapy and in combination with other therapies across more than 30 tumor types and enrolling more than 16,000 patients. Immune-related adverse events (irAEs) are expected based on the nature

of the compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action.

1.2.1.1 Pharmaceutical and Therapeutic Background

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 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. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.2.1.2 Preclinical and Clinical Trial Experience

For complete study information, refer to the current Pembrolizumab Investigator's Brochure (IB).

Non-Clinical Toxicology Summary

In the 1-month and 6-month toxicology study in cynomologus monkeys, pembrolizumab, intravenously administered once a week and once every other week respectively up to a dose of 200mg/kg, resulted in no adverse treatment-related effects. In tissue cross-reactivity studies of pembrolizumab in human and monkey tissues, the expected on-target staining of mononuclear leukocytes membranes was demonstrated in both species. Off-target cross-reactivity staining was also noted in both species but was limited to the cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to experimental methodological artifacts, i.e. tissue processing for IHC, which are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

There was no impact seen on male or female fertility based on evaluation of the Cynomolgus monkeys used in the 1-month and 6-month studies. Reproductive risk assessment was performed using a literature-based approach. In light of the identified potential risk related to inhibition of the PD-1 pathway, no reproductive or developmental toxicity studies were conducted with pembrolizumab. Therefore, inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

Clinical Trial Summary

As of the data cutoff dates for Version 11 (01-Sep-2016) of the Pembrolizumab Investigator's Brochure, pembrolizumab monotherapy and combination therapies have been administered to approximately 9833 subjects, with hematologic malignancies and solid tumors, in Merck sponsored trials.

Clinical Pharmacology

The PK profile of pembrolizumab, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Exposure to pembrolizumab is approximately linear in the dose range of clinical relevance (1 to 10 mg/kg and at 200 mg). Furthermore, pembrolizumab has a low potential fo eliciting the formation of ADAs.

Efficacy

For this Pembrolizumab IB (Version 11, 01-Sep-2016), efficacy data are available for a total fo 1572 melanoma subjects treated with pembrolizumab in KN001, KN002, and KN006; 1529 subjects with NSCLC treated with pembrolizumab in KN001 and KN010; and 174 subjects with HNSCC treated with pembrolizumab in KN012.

KN001 was an open-label, Phase 1, first-in-human study conducted to evaluate clinical activity of pembrolizumab as a single agent in two cancers, melanoma and NSCLC. The ORR demonstrated the antitumor activity of pembrolizumab in subjects with melanoma (ipilumumab-naïve and previously treated with ipilumumab).

KN002 was a randomized Phase 2 study comparing two doses of pembrolizumab to investigator's choice chemotherapy in subjects with unresectable or metastatic (advanced) melanoma, who had progressed after prior treatment with IPI and BRAF (and/or MEK) inhibitor in subjects with BRAF-mutant melanoma. The study demonstrated superior PFS for both pembrolizumab treatment arms compared to the chemotherapy control arm. Treatment with pembrolizumab led to an ORR that was >4-fold higher than the response rate fo the chemotherapy control arm. This difference was highly statistically significant.

KN006 was a randomized Phase 3 pivotal study, designed to test whether pembrolizumab was superior to IPI in the co-primary efficacy endpoints of PFS and OS in IPI-naïve subjects with unresectable or metastatic melanoma. This study demonstrated statisticaly significant improvements in OS and PFS for subjects randomized to pembrolizumab compared to subjects randomized to IPI. In the 10 mg/kg treatment groups (Q2W and Q3W), 185 subjects experienced objective responses that ranged from 1.4 months to 8.2 months in duration.

KN010 was a randomized, adaptively designed Phase 2/3 trial of pembrolizumab at 2 dose levels vs docetaxel in subjects with NSCLC with PD-L1 positive tumors, who have experienced disease progression after platinum-containing systemic therapy.

KN012 was a Phase 1b study of pembrolizumab in subjects with advanced solid tumors, including subjects with HPV-negative and HPV-positive head and neck cancer. The primary population for analysis included HNSCC subjects previously exposed to platinum therapy.

The ORRs for pembrolizumab treatment in KN001, KN002, KN006, KN010, and KN012 compared favorably to historical response rates for available treatments for melanoma, NSCLC, and HNSCC, respectively, particularly in subjects who have progressed after multiple prior therapies.

1.2.1.3 Safety Profile

Pembrolizumab is safe and well tolerated, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (3.9%). Furthermore, the frequency of immune-mediated adverse reactions (AEOSIs) is low, and these events are readily managed in the clinical setting.

The safety and efficacy data generated to date provide a favorable benefit-risk assessment for the use of pembrolizumab as a treatment for subjects with advanced/metastatic melanoma, NSCLC, and HNSCC.

There are no specific safety concerns based on the results of nonclinical studies. Pembrolizumab has the same mechanism of action as other anti-PD-1 monoclonal antibodies. Preclinical studies have suggested similar potency, and PK modeling has suggested similar human PK in the class. Accordingly, the AEs observed with other anti-PD-1 antibodies may serve as an indicator for the AEs to expect in cancer subjects.

Pembrolizumab is generally well-tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune-mediated AEs are of primary concern. The important identified risks for pembrolizumab are of an immune-mediated nature, and include the following: pneumonitis; colitis; hepatitis; nephritis; endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism) and Type 1 diabetes mellitus; uveitis; myositis; Guillain-Barré syndrome; pancreatitis; and severe skin reactions. Information on the nature and frequency of these identified risks is included in the Reference Safety Information of Version 11 of

the Investigator's Brochure. The majority of immune-mediated adverse events were mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy.

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

Further details regarding reporting and management of immune-related AEs (irAEs) in general are described below.

In addition to the immune-related risks noted above, infusion-related reactions are also an important identified risk for pembrolizumab; however, they are not considered immune-mediated. Information regarding the nature and frequency of infusion-related reactions is included in the Reference Safety Information in Version 11 of the Investigator's Brochure.

Immune-Related Adverse Events

Based on the mechanism of action of pembrolizumab and similar immunomodulatory agents, the Sponsor is interested in all potential irAEs, and encourages appropriate investigation of signs and symptoms suggestive of these.

Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and infrequently require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants.

Table 1.2.1.3.1 All AEOSI Adverse Reactions Considered Expected for Pembrolizumab

Adverse Reaction	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Subjects in population	**2799**	
Immune-Mediated Adverse Reactions		
Hypothyroidism	**237**	**(8.5)**
Hypothyroidism	236	(8.4)
Myxoedema	1	(0.0)
Primary hypothyroidism	1	(0.0)
Hyperthyroidism	**96**	**(3.4)**
Hyperthyroidism	96	(3.4)
Pneumonitis	**94**	**(3.4)**
Pneumonitis	87	(3.1)
Interstitial lung disease	7	(0.3)
Colitis	**49**	**(1.8)**
Colitis	46	(1.6)
Colitis microscopic	2	(0.1)
Enterocolitis	1	(0.0)
Severe skin reactions	**38**	**(1.4)**
Rash	9	(0.3)
Rash maculo-papular	7	(0.3)
Pruritus	4	(0.1)
Lichen planus	2	(0.1)
Pemphigoid	2	(0.1)
Psoriasis	2	(0.1)
Rash generalised	2	(0.1)
Contusion	1	(0.0)
Dermatitis	1	(0.0)
Drug eruption	1	(0.0)
Erythema	1	(0.0)
Erythema multiforme	1	(0.0)
Jaundice	1	(0.0)
Pruritus genital	1	(0.0)
Rash erythematous	1	(0.0)

(Presented by Decreasing Frequency of AEOSI Category)

cont. Table 1.2.1.3.1 All AEOSI Adverse Reactions Considered Expected for Pembrolizumab (Presented by Decreasing Frequency of AEOSI Category)

Adverse Reaction	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Rash pruritic	1	(0.0)
Rash pustular	1	(0.0)
Skin lesion	1	(0.0)
Stevens-Johnson Syndrome	1	(0.0)
Hepatitis	**19**	**(0.7)**
Autoimmune hepatitis	12	(0.4)
Hepatitis	6	(0.2)
Drug-induced liver injury	2	(0.1)
Hypophysitis	**17**	**(0.6)**
Hypophysitis	9	(0.3)
Hypopituitarism	8	(0.3)
Uveitis	**14**	**(0.5)**
Uveitis	10	(0.4)
Iridocyclitis	2	(0.1)
Iritis	2	(0.1)
Myositis	**11**	**(0.4)**
Myositis	7	(0.3)
Myopathy	3	(0.1)
Rhabdomyolysis	1	(0.0)
Pancreatitis	**9**	**(0.3)**
Pancreatitis	7	(0.3)
Autoimmune pancreatitis	1	(0.0)
Pancreatitis acute	1	(0.0)
Type 1 diabetes mellitus	**6**	**(0.2)**
Type 1 diabetes mellitus	5	(0.2)
Diabetic ketoacidosis	2	(0.1)
Nephritis	**4**	**(0.1)**
Tubulointerstitial nephritis	4	(0.1)

cont. Table 1.2.1.3.1 All AEOSI Adverse Reactions Considered Expected for Pembrolizumab (Presented by Decreasing Frequency of AEOSI Category)

Adverse Reaction	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Guillain-Barre Syndrome	**2**	**(0.1)**
Axonal neuropathy	1	(0.0)
Guillain-Barre syndrome	1	(0.0)
Secondary adrenal insufficiency	**1**	**(0.0)**
Secondary adrenocortical insufficiency	1	(0.0)
Non Immune-Mediated Adverse Reactions		
Infusion related reactions	**70**	**(2.5)**
Infusion related reaction	29	(1.0)
Hypersensitivity	22	(0.8)
Drug hypersensitivity	13	(0.5)
Anaphylactic reaction	3	(0.1)
Cytokine release syndrome	2	(0.1)
Serum sickness	1	(0.0)

KN = KEYNOTE; MedDRA = Medical Dictionary for Regulatory Activities
Every subject is counted a single time for each applicable row and column.
MedDRA version used is 18.1.
[a] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010 .
(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).

Nephritis: Five additional cases of the AEOSI nephritis were observed in the Reference Safety Dataset; however, they are not contained in the preceeding table because the reported AE coding at the time did not include an AEOSI nephritis term. The coding for each of these 5 cases has since been updated after the data-lock of the Reference Safety Dataset as follows, and each of the terms below is considered an AEOSI adverse reaction expected for pembrolizumab:

- Tubulointerstitial nephritis: n=2 (in addition to 4 cases already included in above table), for an overall frequency of n=6 (0.2%)
- Nephritis: n=2 (0.1%)
- Autoimmune nephritis: n=1 (0%)

Therefore, based on the addition of the above 5 cases, the overall frequency for the AEOSI nephritis in the Reference Safety Dataset should be n=9 (0.3%)

Colitis: One event in the Reference Safety Dataset was initially counted as an AEOSI of colitis. However, it was later determined that the subject did not have colitis, and had been included in the Reference Safety Dataset summary of colitis due to data entry errors. Therefore, the overall frequency of the AEOSI colitis should be n=48 (1.7%), and the frequency for the individual event of colitits should be n=45 (1.6%)

Infusion-Related Reactions: One subject had an event of anaphylactoid reaction that was not counted as an infustion-related reaction since this term was not part of the terms list for the AEOSI infusion-related reactions at the time of reporting. Therefore, the incidence of AEOSI infusion-related reactions in the Referense Safety Dataset should be n=71 (2.5%). The term “anaphylactoid reaction” (n=1 [0%]) is considered an AEOSI expected for pembrolizumab.

Table 1.2.1.3.2 All Additional Adverse Reactions Considered Expected for Pembrolizumab

Preferred Term	Frequencies Reference Safety Dataset for MK-3475[a] n	(%)
Subjects in population	2799	
Diarrhoea	625	(22.3)
Cough	615	(22.0)
Pruritus	562	(20.1)
Arthralgia	504	(18.0)
Rash	499	(17.8)
Pyrexia	357	(12.8)
Back pain	349	(12.5)
Abdominal pain	274	(9.8)
Vitiligo	171	(6.1)
Hyponatraemia	146	(5.2)

KN = KEYNOTE; MedDRA = Medical Dictionary for Regulatory Activities

Every subject is counted a single time for each applicable row and column.

MedDRA version used is 18.1.

Individual PTs were identified from KN002, KN006, and KN010. Each PT occurred at a rate of ≥ 10% in at least one of these studies in patients treated with MK-3475 and at a higher incidence than in the control arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grade 3 or higher])

[a] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

1.2.1.4 Dose Selection

PN001 is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. 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 pembrolizumab 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, will be 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 pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab 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 pembrolizumab 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. Pembrolizumab 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 pembrolizumab 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.

1.2.2 Lanreotide Depot

Lanreotide is an octapeptide analogue of somatostatin.

1.2.2.1 Pharmaceutical and Therapeutic Background

Lanreotide is a well-established peptide analogue of the natural hormone somatostatin, in which the biochemical stability of the peptide has been increased by incorporation of modified amino acids. Like native somatostatin, lanreotide inhibits the secretion of many hormones (including GH), and has anti-proliferative activity. Somatostatin is a peptide naturally produced by the hypothalamus and neurons of the GI tract. Somatostatin produced by the hypothalamus acts on the pituitary gland to inhibit the synthesis and release of GH and thyroid stimulating hormone (TSH). Therefore, in diseases involving increases of GH, such as acromegaly and some cancers, somatostatin has a use in inhibiting GH production. Somatostatin produced by neurons of the GI tract acts to inhibit numerous digestive

endocrine and exocrine secretions. Therefore, the compound can also inhibit secretions from digestive fistulae which, if left untreated, prevent fistula closure leading to risk of skin damage and sepsis.

Receptors for somatostatin are expressed on the surface of most NETs, and since somatostatin inhibits cell proliferation, the compound can also be used to treat these tumors. The therapeutic use of somatostatin is, however, limited by its short halflife of only 2 to 3 minutes. Therefore, synthetic SSAs with increased specificity and half-life duration have been developed for medicinal use. Lanreotide is a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin. The compound is characterised by the presence of D-Tryptophan in the amino acid ring, increasing stability, and by the presence of D-beta Nal outside of this ring, which increases its selectivity. The terminal amine function reduces binding to central nervous system (CNS) receptors. Lanreotide exhibits high affinity for the somatostatin Type 2 (SSTR2) and Type 5 (SSTR5) receptors found in the pituitary gland, GH secreting pituitary tumors, NETs and the digestive tract. The product has a much lower affinity for somatostatin Type 1, 3 and 4 receptors.

Lanreotide has been developed in the following formulations:

- Immediate release
- Microparticle prolonged release (lanreotide PR 30 and 60 mg)
- Lanreotide Autogel 60, 90 and 120 mg

Marketing authorisation has been granted for lanreotide MPF (indicated for the treatment of acromegaly, NETs, and also for thyrotropic adenoma and digestive fistulae in some countries), and for lanreotide Autogel formulation (indicated for acromegaly and NETs). The immediate release formulation (IRF) is not registered. The lanreotide PR 30 mg (MPF) is administered by intramuscular (i.m.) injection every 7, 10 or 14 days. The 7-day dose interval is only registered in a few countries, and the lanreotide PR 60 mg formulation, a monthly formulation, is no longer registered in any country.

Lanreotide Autogel was developed to extend the duration of lanreotide release, obtaining at least a 28-day dosing interval. This formulation can be administered by deep subcutaneous injection into the external quadrant of the buttock by a healthcare professional. A clinical variation has been approved in several countries, whereby patients who are well controlled by SSAs can be treated with lanreotide Autogel 120 mg every 42 to 56 days rather than every 28 days.

Lanreotide Autogel was first launched in France in 2001, and is registered in approximately 60 countries worldwide including countries in Africa, Asia, Central and Eastern Europe, the Middle East, Australasia, and North, Central and South America.

Lanreotide depot for injection is available as 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL single-use prefilled syringes

Lanreotide depot injection is a somatostatin analog indicated for: 1) the long-term treatment of acromegalic patients who have had aninadequate response to or cannot be treated with surgery and/orradiotherapy; and 2) the treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic gastroenteropancreaticneuroendocrine tumors (GEP-NETs) to improve progression-free survival.

1.2.2.2 Preclinical and Clinical Trial Experience

For complete study information, refer to the Lanreotide Investigator's Brochure (IB).

Non-Clinical Toxicology Summary

Toxicology data have been assessed based on plasma lanreotide concentrations in animals compared with humans after administration of lanreotide Autogel 120 mg (1.7 mg/kg based on a body weight of 70 kg).

The toxicity of lanreotide was extensively studied in rodents and dogs and no acute or chronic toxicity hazard was detected. Repeated subcutaneous injection of lanreotide Autogel for up to 26 weeks in rats and up to 39 weeks in dogs did not cause systemic target organ toxicity at plasma concentrations of approximately 200- to 400-fold (rats) and 16- to 23-fold (dogs), the exposure observed after administration of lanreotide Autogel 120 mg to humans. Chronic administration of lanreotide produced a reduction in growth rate (decreased body weight gain, decreased weight of some organs) in rats and dogs and gallbladder dilatation in dogs which were considered related to the pharmacological activity of the product.

The effects on the GI tract of animals were similar to those in humans. No overt signs of pancreatic or gallbladder toxicity were observed in the chronic toxicity studies in rats and dogs.

In standard tests, lanreotide showed no tendency to cause damage to deoxyribonucleic acid (DNA). Two-year rodent carcinogenicity studies of lanreotide administered once daily by subcutaneous injection did not result in systemic neoplastic changes despite achieving 12- to 30-fold (at 10 mg/kg/day in mice) and 2.5- to 2.7-fold (at the highest dose tested of 0.5 mg/kg/day in rats) the human plasma concentration after administration of the MRHD of 120 mg. An increase in neoplastic changes with lanreotide compared to controls was observed at the injection sites for doses of approximately 20- and 90-fold (mice) and 1.8-fold (rats) the human plasma level at the MRHD. The neoplastic changes observed at the injection site of rodents were probably caused by long-term irritation of the subcutaneous tissue rather than damage to DNA and are not considered a cause for concern with regard to the safe use of lanreotide Autogel in patients.

Reproductive toxicity studies in rats and rabbits showed that lanreotide did not interfere with normal embryonic development in pregnant animals despite the presence of lanreotide metabolites in the amniotic fluid and foetal tissues. There was a tendency to reduce female fertility but only at doses that reduced body weight gain. At these doses this effect is an expected outcome of inhibition of GH secretion. The fertility of males was unaffected by the treatment and the behavioural and reproductive characteristics of 2 subsequent generations were unaffected by administration of the drug to the parents despite the excretion of unchanged lanreotide and 1 of its metabolites in the maternal milk.

The local tolerance of lanreotide Autogel after chronic subcutaneous injection in rats and dogs revealed the presence of nodules at the injection site after each administration. The histopathological changes (granulomatous inflammation and/or fibrosis) observed at the injection site following lanreotide Autogel administration appear to be a normal reaction of the subcutaneous tissue to the presence of a foreign body.

Studies with lanreotide Autogel or IRF indicate that lanreotide is not harmful to the immune system of animals. Lanreotide causes less stimulation to the immune system of humans than in rats and dogs. Toxicology studies of the impurities present in lanreotide Autogel were conducted using high doses compared to those intended for human use. No safety concerns were identified during these studies.

Based upon the pharmacology, PK, safety pharmacology and toxicology studies (including cardiovascular tolerance), lanreotide Autogel is considered to be safe for chronic use in humans.

Clinical Trial Summary

In terms of NET, the main effects of lanreotide are reducing carcinoid syndrome symptoms associated with NET and tumor stabilization. As of May 14, 2014 (Lanreotide IB Version 14.0), the main efficacy parameters used to assess the effect of lanreotide in NET studies were the number of symptom episodes (mainly diarrhoea and flushing) and PFS. Reductions in tumor biomarkers have also been observed in patients with NET.

The efficacy of lanreotide Autogel (60, 90 and 120 mg) in the treatment of symptoms associated with carcinoid NET was investigated in an open, multicentre, dose titration clinical study (Study 718). Lanreotide Autogel was administered by deep subcutaneous injection at 4-week intervals for 6 months to assess the relief of clinical symptoms in patients diagnosed with symptomatic carcinoid NET. Seventy-one patients were treated and included in the ITT population, 35 were included in the Per Protocol (PP) population, and 71 were included in the Safety population. The primary efficacy endpoint of the study was the proportion of patients whose target symptom responded at Month 6. The investigator identified the symptom that was most troublesome to each patient and this became the "target symptom". A response was defined as a reduction of ≥50% in the mean daily number of episodes of the target symptom (i.e., the number of episodes of diarrhea or the number of episodes of moderate or severe flushing) compared with baseline. Symptom assessments were recorded in patient diaries. The response rate was approximately 40%.

The secondary efficacy analyses included an evaluation of the efficacy of lanreotide Autogel in the relief of clinical symptoms (diarrhoea and/or flushing) after each month of treatment. The changes from baseline for both flushing and diarrhoea were clinically and statistically significant for each month (Months 1 to 6). In Study 166, 9/30 patients had NET-related symptoms at baseline; after lanreotide treatment, symptoms were totally controlled in 4 of these patients.

A long-term retrospective study has been conducted with lanreotide Autogel in patients with malignant carcinoid syndrome, assessing clinical and objective response and tolerance. A 9-year study included 76 patients with metastatic midgut NETs and carcinoid syndrome. Clinical response was based on symptom score with radiological assessment based on RECIST (Response Evaluation Criteria In Solid Tumors). In this study, lanreotide Autogel provided good symptomatic control of diarrhoea and flushing in patients with malignant carcinoid syndrome.

Another phase III study (Study 726) has been completed, which investigated the effect of lanreotide Autogel 120 mg on PFS in patients with well- or moderately well-differentiated, non-functioning entero-pancreatic, neuroendocrine tumors.

1.2.2.3 Safety Profile

The safety results from NET studies were similar to those from acromegaly studies. The most common treatment emergent adverse events (TEAEs) were GI disorders, including diarrhea and abdominal pain. Other common TEAEs were asthenia, fatigue, headache, vomiting, nasopharyngitis, nausea, anorexia, cholelithiasis, flatulence, intestinal obstruction, injection site pain, back pain, hyperglycaemia and dizziness.

1.2.1.4 Dose Selection

According to prescribing information (revised date 12/2004), the recommended dose of lanreotide depot is 120 mg administered every 4 weeks by deep subcutaneous injection. There is no recommended dose adjustment for mild or moderate renal impairment. There is insufficient information to recommend a dose for patients with severe renal impairment or with hepatic impairment of any severity. However, in order to match the lanreotide dosing to the dosing of pembrolizumab (every 3 weeks), a dose of 90mg

administered every 3 weeks (same dose intensity as the 120mg every 4 week dose) by deep subcutaneous injection will be used for the current study.

1.3 Study Rationale

In the proposed study, we aim to study the combination of pembrolizumab with lanreotide depot (the formulation available in the US) in patients with unresectable, recurrent, or metastatic GEP-NETs, who have had progression in the prior 12 months in order to establish that full dose of each agent is tolerable in combination and to explore the clinical activity of this combination on outcome measures including response rate, disease free survival/progression free survival, and overall survival, and we will also study the side effect profile of pembrolizumab in this setting. Furthermore, in order to understand the effect of pembrolizumab and lanreotide depot on immune parameters, we will explore the effect of this combination on circulating immune cells and determine correlations of clinical parameters with PD-L1 expression in tumor.

The response rate to lanreotide depot was not reported in the final publication of the CLARINET trial but in a prior study of lanreotide (9) one of 25 patients experienced a partial response to single agent and two of 28 patients experienced a response to interferon plus lanreotide depot. In a more recent study, the response rate was 4% (11). Therefore, the response rate to lanreotide depot is likely to be 10% or less. Further, this study may enroll patients who have previously progressed on somatostatin analogues so it is unlikely that lanreotide depot alone will lead to clinical responses in these patients. The response rate to pembrolizumab for neuroendocrine tumors is not reported as there have been few patients with neuroendocrine tumors treated with pembrolizumab. Thus far, the malignancies for which anti-PD-1 therapy is indicated or will likely become indicated have demonstrated greater than 10% response rates and in general, response rate of 20% or greater. With the projected number of participants (n=26), the difference between 10% and 25% in the proportion of patients responding can be detected with adequate power.

Because the immune profile (including regulatory T cells, myeloid derived suppressor cells, T cell subsets, dendritic cells) in the peripheral blood of neuroendocrine tumor patients in general and the immune response to anti-PD-1 therapy in these patients in particular have not been well described, we will analyze these cell populations in the peripheral blood of patients on the clinical trial (12). Further, because the validity of PD-L1 as a biomarker of response to anti-PD-1 antibody therapy is still under evaluation and has been observed to be associated with outcome in some tumors but not others (13), we propose to correlate clinical responses (tumor regression) with PD-L1 expression within pre-treatment tumor specimens.

2.0 OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is:

1. To evaluate the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to pembrolizumab in combination with lanreotide depot in subjects with progressive, advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

2.2 Secondary Objectives

The secondary objectives of this trial are:

1. To assess the safety of pembrolizumab in combination with lanreotide depot in subjects with GEP-NETs.

2. To assess progression free survival (PFS) of pembrolizumab in combination with lanreotide depot in subjects with GEP-NETs.

3. To assess the overall survival (OS) of pembrolizumab in combination with lanreotide depot in subjects with GEP-NETs.

4. To evaluate the ORR by Immune-Related Response Criteria (irRC) to pembrolizumab in combination with lanreotide depot in subjects with progressive, advanced or metastatic GEP-NETs.

2.3 Exploratory Objectives

The exploratory objectives of this trial are:

1. To characterize changes in circulating immune cells in subjects with GEP-NETs treated with pembrolizumab in combination with lanreotide depot.

2. To determine whether safety and efficacy parameters (ORR, PFS, OS) correlate with PD-L1 expression within the tumor in pre-treatment specimens.

3. To explore the correlation between blood-based biomarkers and clinical outcomes.

3.0 STUDY DESIGN

3.1 Study Description

This open-label, non-randomized, phase II trial is designed to assess the safety and efficacy of pembrolizumab in combination with lanreotide depot in patients with progressive, advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) who have progressed on front line somatostatin analogue (SSA) therapy.

The study will be conducted in two stages: 1) Safety Run-In Cohort and 2) Expanded Cohort.

1. *Safety Run-In Cohort*: The first stage is a safety run-in cohort of patients treated with pembrolizumab 200 mg intravenous (IV) every 3 weeks and lanreotide depot 90mg subcutaneous (SQ) every 3 weeks (+/-7 day treatment window). Up to 6 patients at the Duke Cancer Institute will be accrued at the starting dose level. If one or less subject meets treatment-related discontinuation criteria (refer to Section 5.7) during Cycle 1, then the study will proceed to the second stage, Expanded Cohort. If more than one subject meets treatment-related discontinuation criteria (refer to Section 5.7) during Cycle 1, then the study will be redesigned to include alternative dose levels.

2. *Expanded Cohort*: The second stage is an expanded cohort of up to 20 patients enrolled at the Duke Cancer Institute and select Duke Cancer Network sites. Patients will be treated with pembrolizumab 200mg IV every 3 weeks and lanreotide depot 90mg SQ every 3 weeks as determined by the Safety Run-In Cohort.

After informed consent is obtained, patients will complete baseline and screening evaluations (refer to Section 5.1) to ensure subject eligibility requirements (refer to Section 4.0) are met prior to starting study drug regimen. Patients who meet eligiblity will start the first cycle of the study drug regimen (see to Table 3.1 below). The cycle length is 21 days.

Safety assessments (refer to Section 5.2) will be performed on Day 1 of each cycle, as clinically indicated, and until 30 days after the last dose of study drug. Study procedures (refer to Study Calendar in Appendix D) include physical examination, laboratory tests and adverse events review using NCI CTCAE version 4.0.

Efficacy (refer to Section 5.6) will be assessed by radiographic imaging (CT and/or MRI) every 4 cycles (ie. every 12 weeks) using RECIST version 1.1 and irRC.

Patients may continue to receive the study drug regimen until they experience unacceptable treatment-related toxicity, disease progression, or once they have been treated for 2 years (or received 35 administrations of pembrolizumab) at which time they will revert to commercial use of lanreotide depot alone (may use 120mg every 4 weeks at their physician's discretion) without pembrolizumab.

Patients will be followed for survival for up to 48 weeks after the last subject has finished the study drug regimen.

Tumor tissue and peripheral blood for correlative studies will be collected from all patients (refer to Section 8.0).

Table 3.1 Cohorts

Cohorts	# Evaluable Subjects	Pembrolizumab IV Every 3 Weeks	Lanreotide Depot SQ Every 3 Weeks
Safety Run-In*	6	200mg	90mg
Expanded	20	200mg	90mg

* Alternative dosing levels or schedules may be explored if more than one subject meets discontinuation criteria, then the study will be redesigned to include alternative dose levels.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

1. Willing and able to provide written informed consent for the trial.

2. At least 18 years of age on day of signing informed consent.

3. Non-resectable, recurrent, or metastatic well- or moderately-differentiated gastroenteropancreatic neuroendocrine tumor (GEP-NETs) with disease progression within the last 12 months. (Patients who have received prior local therapy, including but not limited to embolization, chemoembolization, radiofrequency ablation, radiation therapy, are eligible provided that measurable disease falls outside the treatment field or within the field but has shown an increase of > 20% in the size. Prior local therapy must be completed at least 4 weeks prior to the baseline scan.)

4. Prior somatostatin analogue therapy. (Patients should receive the first dose of study drug no sooner than 4 weeks from the last dose of somatostatin analogue.)

5. At least one measurable lesion based on RECIST version 1.1.

6. Agrees to provide available archived tumor tissue specimen. (Patients who do not have available archived tumor must agree to have core or excisional biopsy of a tumor lesion obtained up to 42 days prior to the first dose of study drug, if safely accessible. If archived tissue is not available and the tumor is not amenable to safe biopsy, subject is still eligible to participate.)

7. ECOG performance status of 0 or 1 (refer to Appendix C).

8. Adequate organ function defined as:

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 EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** calculated creatinine clearance (CrCL) per institutional standard (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
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 2.5 mg/dL

9. Negative serum pregnancy test within ≤ 7 days prior to the first dose of study drug, for women of childbearing potential only.

10. Female subjects agree to use two birth control methods, be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study drug.

11. Male subjects agree to use an adequate method of contraception for the course of the study through 120 days after the last dose of study drug.

4.2 Exclusion Criteria

1. Tumor mitotic rate >20/10 hpf and/or Ki67 index >20% (if available).

2. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study drug.

3. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

4. Known history of active TB (Bacillus Tuberculosis).

5. Hypersensitivity to pembrolizumab or lanreotide or any of their excipients.

6. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of study drug or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

7. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the first dose of study drug or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

8. Prior major surgery within 2 weeks prior to the first dose of study drug or who has not recovered adequately from the toxicity and/or complications from the intervention.

9. 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.

10. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. 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 at least 7 days prior to the first dose of study drug. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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

12. Known history of, or any evidence of active, non-infectious pneumonitis.

13. Active infection requiring systemic therapy.

14. 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 physician.

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

16. 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 study drug.

17. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

18. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

20. Live vaccine within 30 days of planned start of study drug regimen. 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.

21. History of intolerance to somatostatin analogues.

4.3 Inclusion of Women and Minorities

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

5.0 STUDY ASSESSMENTS

Note: After Cycle 1, if the subject is unable to have a study assessment or treatment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Refer to Appendix D for **Study Calendar**.

5.1 Screening Period

During the Screening Period, subjects are consented and screened for the study. Informed consent must be obtained before initiation of any screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the local Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) policies. Study eligibility is based on meeting all of the inclusion criteria and none of the exclusion criteria (refer to Section 4.0) before the first dose of study drug on Cycle 1 Day 1.

The following study procedures must be done within 28 days prior to Cycle 1 Day 1:

- Demographics
- Medical and cancer history
- Physical examination
- Height
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Thyroid function tests
- Adverse event assessment (review of baseline symptoms)
- Tumor assessment (CT and/or MRI scans)
- Chromogranin A (blood tumor marker)
- Tumor tissue (archived tumor if available. If archived tissue is not available, a fresh tissue biopsy will be attempted provided that the subject has tumor amenable to safe biopsy. If archived tissue is not available, and subject does not have tumor amenable to safe biopsy, they are still eligible to participate).

- Circulating immune cells
- Protein multiplex arrays

The following study procedures must be done within 7 days prior to Cycle 1 Day 1:

- CBC with differential
- Chemistries including liver function tests (LFTs)
- Urinalysis
- Serum pregnancy test for women of childbearing potential

Subject eligibility is determined using lab results obtained up to 7 days prior to Cycle 1 Day 1. Any laboratory assessments repeated on Cycle 1 Day 1 must meet eligibility requirements. The Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study.

5.2 Treatment Period

During the Treatment Period, subjects will receive pembrolizumab on Day 1 and lanreotide depot on Day 1 of each 21-day cycle until either: 1) disease progression; 2) the occurrence of unacceptable treatment-related toxicity; 3) completion of 2 years of study treatment (or 35 administrations of pembrolizumab); or 4) other reason(s) for subject discontinuation as described in Section 5.7. Toxicity-related dose modifications of pembrolizumab and lanreotide may occur during the Treatment Period. Dose modification guidelines are described in Section 7.1.

In each cycle after Cycle 1, subjects will have study procedures on Day 1, +/-7 days and may have laboratory assessments obtained up to 3 days prior to the treatment visit. If clinically indicated, additional visits and/or safety assessments may be warranted.

The following study procedures must be completed on Day 1 of each cycle (±7 days):

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs
- Urinalysis
- Pembrolizumab and Lanreotide administration

The following study procedures must be completed every 12 (± 1) weeks:

- Thyroid function tests
- Serum pregnancy test for women of childbearing potential
- Tumor assessment (CT and/or MRI scans)
- Chromogranin A (blood tumor marker)
- Circulating immune cells - first restaging only
- Protein multiplex arrays

Restaging scans will be performed every 4 cycles (ie. every 12 weeks) and disease reponse will be assessed using guidelines described in Section 5.6.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Follow-up Period.

5.3 Follow-up Period

Subjects should return 30 (±7) days after their last dose of study drug for an off-treatment visit to complete the following study procedures:

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs
- Urinalysis
- Thyroid function tests (if clinically indicated)
- Serum pregnancy test for women of childbearing potential
- Circulating immune cells
- Protein multiplex arrays

Additional follow-up may occur for subjects with adverse events (AEs) related to study drug that are ongoing at the time of this off-treatment visit unless AE is deemed unresolveable or subject has started a new anti-cancer treatment regimen.

For subjects that are discontinued from study treatment for reasons other than disease progression, subjects will have disease status (chromogranin A and restaging scans per standard of care schedule) followed until disease progression or start of new anti-cancer treatment regimen. Disease status may be collected by personal interviews or review of medical records.

Subjects will be followed for survival for up to 48 weeks after the last subject has finished study drug regimen or until the study is closed (whichever comes first). Survival status may be collected by personal interviews or review of medical or public records.

5.4 Laboratory Assessments

Local laboratories will perform all clinical laboratory tests using standard procedures, and results will be provided to the Investigator. Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose modification, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the case report form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious adverse event (SAE).

Refer to Appendix E for details of laboratory tests for this study. In addition, chromogranin A, a blood tumor marker, will be obtained at baseline and at every restaging.

5.5 Adverse Event Assessment

AE definition is described in Section 10.1. AEs will be documented throughout the study. AE seriousness, grade, and relationship to study drug will be assessed by the Investigator using NCI CTCAE version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

SAE definitions and reporting requirements are described in Section 10.2.

Select non-serious and serious adverse events also known as Events of Clinical Interest (ECI) must be recorded and reported as described in Section 10.3.

5.6 Tumor Assessments

Tumor response will be assessed using RECIST version 1.1 and irRC. Radiographic imaging will be performed with CT scan of chest/abdoment/pelvis with and without contrast and/or MRI scan of abdomen/pelvis every 12 (±1) weeks or every 4 cycles after the start of study treatment. The same method for tumor assessment should be employed at every assessment.

5.6.1 RECIST version 1.1

RECIST is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progression") during treatments. The original criteria were published in February 2000 by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States and the National Cancer Institute of Canada Clinical Trials Group. RECIST 1.1, published in January 2009, is an update to the original criteria and will be used for this study.

Refer to Appendix A for definition of target lesions, methods of measurement and all other related criteria for RECIST version 1.1. The following summarizes the definitions of the criteria used to determine objective tumor response for target lesions:

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

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

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

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

5.6.2 Immune-Related Response Criteria

The responses that are seen with immunotherapeutic agents may extend beyond those of cytotoxic agents and could include responses after disease progression that is not captured by RECIST. To

account for this, for this study, immune-related response criteria (irRC) will be used to allow for more comprehensive evaluation of clinical activity. Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because PD (progressive disease) by initial radiographic evaluation does not necessarily reflect therapeutic failure, thus stopping the study treatment with initial perceived PD may be premature.

Refer to Appendix B for definitions and guidelines of the irRC. The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- **irCR:** complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- **irPR:** decrease in tumor burden ≥50%relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- **irSD:** not meeting criteria for irCR or irPR, in absence of irPD
- **irPD:** increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

5.7 Subject Discontinuation

Subjects will receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation or withdrawal from trial will be recorded.

Reasons for subject discontinuation by the Investigator may include, but are not limited to, the following:

- Death
- Confirmed radiographic disease progression (Note: With approval of the Lead PI, a subject may be granted an exception to continue on study treatment with confirmed radiographic progression if clinically stable or clinically improved.)
- Completed 2 years of study treatment or 35 administrations of pembrolizumab
- Significant noncompliance by subject or Investigator
- Investigator or Lead PI determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Withdrawal of consent
- Lost to follow-up
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted methods of contraception during the course of the study and for 120 days following the last dose of study drug
- Women who become pregnant or are breast feeding
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol

- The following **Treatment-Related Discontinuation Criteria** attributed to pembrolizumab, lanreotide depot, or both:
  - Any Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 OR requires systemic treatment.
  - Any Grade 3 non-skin adverse event lasting > 7 days, with the following exceptions for treatment-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
    - Grade 3 uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of *any duration* requires discontinuation
    - Grade 3 laboratory abnormalities do not require treatment discontinuation except Grade 3 thrombocytopenia > 7 days OR associated with bleeding requires discontinuation
  - Any liver function test (LFT) abnormality that meets the following criteria:
    - AST or ALT > 8 x ULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
  - Any Grade 4 adverse event or laboratory abnormality, except for the following events:
    - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset
    - Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered
  - Any dosing interruption lasting > 6 weeks with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage treatment-related adverse events are allowed
    - Dosing interruptions > 6 weeks that occur for non-treatment-related reasons may be allowed
  - Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued pembrolizumab or lanreotide depot dosing

6.0 STUDY DRUGS

6.1 Treatment Compliance and Study Drug Accountability

The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug

accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.2 Pembrolizumab

Pembrolizumab will be provided for this study by Merck & Co., a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use Type I glass vial containing 50 mg of pembrolizumab. The product is preservative-free, white to off-white powder and free from visible foreign matter. It is reconstituted with 2.3 mL sterile water for injection (WFI) to yield a 2.4 mL solution containing 25 mg/mL of pembrolizumab. The reconstituted vial contains an excess fill of 10 mg (equivalent to 0.4 mL of reconstituted solution) to ensure the recovery of label claim of 50 mg pembrolizumab per vial (equivalent to 2 mL of reconstituted solution).

6.2.1 Storage and Handling

Pembrolizumab Powder for Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C). Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F) for up to 24 hours. Following reconstitution with sterile water for injection, Pembrolizumab infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent and the final concentration of pembrolizumab in the infusion solutions should be between 1 mg/mL and 10 mg/mL. If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible. The preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

Refer to Pembrolizumab Pharmacy Manual for additional drug product stability and handling guidelines.

6.2.2 Administration

Pembrolizumab 200 mg will be administered in an outpatient setting as a 30 minute IV infusion on Days 1 of each cycle (+/-7 days for C2 and all subsequent cycles). Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Refer to Pembrolizumab Pharmacy Manual specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

6.3 Lanreotide Depot

Lanreotide depot will be provided by Ipsen. It is provided in a single-dose, prefilled syringe affixed with an automatic needle protection system. The prefilled syringes contain a white to pale yellow, semi-solid formulation.

6.3.1 Storage and Handling

Lanreotide depot must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package. Thirty (30) minutes prior to injection, the sealed pouch of lanreotide depot must be removed from the refrigerator to allow it to come to room temperature. The pouch should remain sealed until injection.

Each syringe is intended for single use and not be used beyond the expiration date on the packaging.

6.3.2 Administration

Lanreotide depot 90 mg will be administered in an outpatient setting as a deep subcutaneous injection (in the superior external quadrant of the buttock) on Day 1 of each cycle (+/- 7 days for C2 and all subsequent cycles). The injection site should be alternated between the right and left sides from one injection to the next.

6.4 Concomitant Medications/Vaccinations

Concomittant medications will be documented throughout the study. Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Lead PI should discuss any questions regarding this with the Merck Clinical team.. The final decision on any supportive therapy or vaccination rests with the Lead PI and/or the subject's primary physician (ie. Investigator).

6.4.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a subject’s welfare may be administered at the discretion of the Investigator in keeping with the local standards of medical care. All concomitant medication received from the date of signed informed consent through 30 days after the last dose of study drug will be documentedincluding all prescription, over-the-counter (OTC), herbal supplements, and IV medications.

Subjects must agree to use two birth control methods after informed consent is signed through 120 days after the last dose of study drug. The two methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation, hysterectomy, or vasectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

6.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or lanreotide depot
- Radiation therapy (Note: Radiation therapy to a symptomatic solitary lesion may be allowed with the approval of the Lead PI.)
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- 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 Lead PI.

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 may describe other medications which are prohibited in this trial.

There are no prohibited therapies during the Follow-up Period.

7.0 DOSE MODIFICATION AND TOXICITY MANAGEMENT

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study drug. Subjects will be instructed to notify their treating physician of any and all AEs. Toxicity will be graded according to NCI CTCAE version 4.0.

All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to study drug(s).

7.1 Dose Modifications

Subjects experiencing one or more AEs due to the study drug(s) may require dose modification(s) as described in Section 7.1.1 and Section 7.1.2. At the discretion of the Investigator, dose modifications are permitted outside of the those provided in the protocol if the Investigator feels it is in the interest of the subject's safety (e.g., due to multiple toxicities, persistent toxicities, intercurrent illness, or short term compliance or monitoring issues, etc.).

Subjects may need to be followed at least weekly when any study drug is held for toxicity until the toxicity returns to Grade ≤ 1 or is determined to be chronic or irreversible.

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, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption, unless otherwise discussed with the Lead PI. The reason for interruption should be documented in the patient's study record.

If pembrolizumab is permanently discontinued, the subject will be discontinued from study treatment.

All dose modifications and reasons for modification must be recorded in the CRF.

7.1.1 Pembrolizumab Dose Modifications

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

Pembrolizumab must be withheld for treatment-related toxicities as per Table 7.1.1. There are no dose reductions for pembrolizumab.

Note: Subject must be permanently discontinued for any severe or Grade 3 treatment-related toxicity that recurs or any life-threatening event unless otherwise specified in Table 7.1.1.

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Table 7.1.1 Pembrolizumab Dose Modifications

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue	Permanently discontinue	
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If
	Grade 4	Permanently discontinue	Permanently discontinue	

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and Follow-up
				sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]	Permanently discontinue	
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and Follow-up
	Grade 3 or 4	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 immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician
NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case T1DM).

7.1.1 Lanreotide Depot Dose Modifications

There are no dose modifications for lanreotide depot indicated for the treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) as described in the FDA approved package insert.

7.2 Toxicity Management

Subjects should receive appropriate supportive care measures as deemed necessary by the Investigator. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. 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.

7.2.1 Pneumonitis

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

- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

7.2.2 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**, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.

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

7.2.3 Diabetes Mellitus

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or **Grade 3-4 Hyperglycemia**, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- Insulin replacement therapy is recommended.

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

7.2.4 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.

7.2.5 Hyperthyroidism or Hypothyroidism

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

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

7.2.6 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.

7.2.7 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.

7.2.8 Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

Table 7.2.8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 7.2.8 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the 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 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1hr of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5hr (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
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 ventilatory 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.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	Subject is permanently discontinued from further trial treatment administration.	

8.0 CORRELATIVES

Biomarkers in patient tumors that can predict response to anti-PD-1 therapy are being actively investigated. One mechanism by which cancer tissues limit the host immune response is via upregulation of PD-1 ligand (PD-L1) and its ligation to PD-1 on antigen-specific CD8+ T cells (12). It appears that PD-L1 expression does correlate with benefit from anti-PD-1 therapy in some malignancies but not others (13). Therefore, it is important to study the PD-L1 expression of the neuroendocrine tumors and whether this correlates with responses or other clinical parameters. Further, although studies thus far have demonstrated fairly limited changes in peripheral blood immune cells following anti-PD-1 therapies (compared with the site of tumors), the dataset on peripheral blood is still fairly limited. In other contexts, neoadjuvant ipilimumab therapy for melanoma, measurement of peripheral myeloid derived suppressor cells (MDSCs) has been associated with progression free survival. Therefore, we propose cytometry by time-of-flight (CyTOF) will be used to analyze changes in the immune cell subtypes that are expected to be altered by treatment. Samples will be acquired, stored and prepared at Duke, and transferred to the University of North Carolina (UNC) and analyzed on their CyTOF machine and the data regarding immune cell markers will be transferred back to Duke. Only subject ID numbers will be shared with UNC. No clinical data or PHI will be transferred. CyTOF analysis destroys the sample, therefore no samples will be retained or re-analyzed at UNC.The CyTOF panels identify immune cell types and related markers for cells of lymphoid and myeloid lineage. The lymphoid panel focuses on T-cell activation, maturation, regulation, and exhaustion. The myeloid panel focuses on myeloid derived suppressor cells (MDSC), M1/M2 polarization, and dendritic cells (DC, pDC). Last, there is limited data on plasma/serum inflammatory marker changes during anti-PD-1 antibody therapy. Individual peripheral blood immune cells will also be analyzed for their production of cytokines by an Isoplexis analysis using an Isoplexis device housed at Duke University. Further, we propose to analyze over 25 cytokines, angiogenesis, and tumor growth factors in plasma to determine changes during therapy.

8.1 Tumor Biomarkers

The level of PD-1 and PD-L1 expression in pre-treatment tumor tissue will be measured by immunohistochemical (IHC) staining at Merck laboratories. Available paraffin embedded tumor tissue from prior biopsies or excisions may used for this study. However, in the event no archival tumor tissue is available, patient will have tumor biopsy performed of safely accessible tumors before starting treatment (within 42 days of starting treatment on this protocol). The preferred type of biopsy is a core biopsy: five 18-gauge core needle biopsies (diameter about 2 mm) with a throw length of approximately 2 cm will provide adequate tissue for study.

Refer to *Study Manual* for collection, processing, and submission details.

8.2 Circulating Immune Cells

Peripheral blood will be collected from each subject at baseline, at first restaging, and at the time of disease progression (or treatment discontinuation) for peripheral blood mononuclear cells (PBMCs). PBMCs will be processed and stored by the Department of Surgery Substrate Services Core Research Support (SSCRS) facility in Medical Sciences Research Building #1.

Refer to *Study Manual* for collection, processing, and submission details.

8.3 Protein Multiplex Arrays

Peripheral blood will be collected from each subject at baseline, at each restaging, at the time of disease progression (or treatment discontinuation) and at 30-day off treatment visit for plasma biomarkers. Plasma will be stored by the Duke Phase I Biomarker Laboratory under the direction of Dr. Andrew Nixon.

Refer to *Study Manual* for collection, processing, and submission details.

8.4 Future Use of Patient Samples

Any remaining biological materials at the end of the study will be deidentified and retained for possible use in biomarker research.

9.0 STATISTICAL ANALYSIS

9.1 General Analysis Considerations

Percentage of PD-L1 + cells by IHC, the percentages of the lymphoid and myeloid cells in peripheral blood, and levels of the cytokines/angiogenesis/inflammatory serum and plasma markers will be listed and summarized using the descriptive statistics (minimum, maximum, mean median, std). The PD-L1 expression and peripheral blood lymphoid and myeloid cell percentages will be correlated with the response by comparing the means of different groups using either 2-sample t-tests or non-parametric Wilcoxon rank-sum test, or the Chi-square test based on the distribution and structure of the data (i.e., either parametric or non-parametric methods will be used depending on the measurement of the corresponding endpoints).

A cohort of patients will be enrolled to assess the primary endpoint of objective response rate (ORR) in this patient population. A safety run-in will be conducted in the first 6 patients enrolled. A starting dose level (full, standard doses of each drug) is planned for this study. If one or fewer subjects meet discontinuation criteria, this dose level will be determined to be safe and the trial will continue. If discontinuation criteria are met in $\geq$ 2/6 patients at the starting dose level, then the study will be redesigned. This study is expected to accrue a minimum of 6 evaluable subjects in the safety run-in portion of the study.

9.1.1 Primary Endpoint

Objective Response Rate (ORR). CT or MRI scans and blood tumor markers will be repeated every two cycles. Tumor response defined as complete response (CR) or partial response (PR) will be assessed using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).

ORR will be estimated by the 90% Exact Lower Confidence Bound (LCB) for the binomial proportion. An ORR of less than 10% will be considered not to be of clinical value, If the 90% LCB is >= 0.1, the regimen will be considered efficacious. With 26 patients studied the LCB will be approximately 0.1 if 5 responses are observed.

If a sufficient number of responses are observed, duration of response (DOR) will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier product-limit method. The median DOR (and two-sided 95% CI) will also be calculated. In addition, the percentage of responders still in response at different time points (3, 6 and 12 months) will be presented based on the KM plot.

The magnitude of reduction in tumor burden will be summarized descriptively (such as a waterfall plot) based on change in the sum of the longest diameters of target lesions relative to baseline.

9.1.2 Secondary Endpoints

PFS: defined as time from start of the treatment until documented disease progression or death from any cause (those for whom event of progression or death not observed will be censored at the time of the last response assessment).

OS: defined as time from start of the treatment till the patient's death from any cause (patient who are still alive at the end of the study will be censored).

If sufficient events are observed, PFS and OS will be estimated by the Kaplan-Meier method.

Safety and Tolerability Monitoring: The safety and tolerability of Lanreotide Depot plus pembrolizumab will be primarily assessed by the rate of treatment-related AEs leading to drug discontinuations during the first 12 weeks of treatment. The regimen will be considered safe if <33% of patients treated require dosing discontinuation for study drug related toxicity in the first 12 weeks (e.g., 0 of 3, ≤1 of 6, ≤ 2 of 9, ≤3 of 12 or ≤5 of 18 patients). This will be assessed continuously throughout the study. A patient will be considered evaluable for safety if treated with at least one dose of study regimen. In addition, safety and tolerability will be analyzed by the incidence of adverse events, serious adverse events, and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Descriptive statistics (counts, percentages) will be used to summarize safety parameters (adverse events, serious adverse events, adverse events leading to discontinuation, deaths) for all treated subjects. Safety summaries will be presented by the severity of the adverse event and by relationship to study drug.

9.1.3 Exploratory Endpoints

Descriptive statistics (minimum, maximum, mean median, std) will be provided for percentage of PD-L1 + cells by IHC, the percentages of the lymphoid and myeloid cells in peripheral blood, and levels of the cytokines/angiogenesis/inflammatory serum and plasma markers.

For analysis of the immune monitoring data from the 2 polychromatic flow cytometry panels, we will perform initial analysis using statistical graphics (e.g. box-plots) of the cell subset relative frequencies and trends over time. To assess the impact of cell subsets of interest (listed in Section 8.0 at baseline and on-treatment on treatment outcome, we will perform a one-way ANOVA of cell subset relative frequency against the RECIST 1.1 response categories to identify variables whose unadjusted p-values are statistically significant. Given the exploratory aim of the research, no correction for the number of independent variables will be performed, and a ranked list of cell subsets with uncorrected p-values will be tabulated. This list will be used for hypothesis generation, and to select candidates for independent validation studies.

The PD-L1 expression and peripheral blood lymphoid and myeloid cell percentages will be correlated with the response by comparing the means of different groups using either 2-sample t-tests or non-parametric Wilcoxon rank-sum test, or the Chi-square test based on the distribution and structure of the data (i.e., either parametric or non-parametric methods will be used as appropriate).

Given the limited sample size, all biomarker analyses will be considered exploratory.

10.0 SAFETY

Refer to *Study Manual* for required reporting forms.

10.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the supporting company product(s), is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Supporting company product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the supporting company for human use.

AEs may occur during the course of the use of supporting company product(s) in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE unless it is considered to be drug related by the Investigator.

AEs will be documented from the date of first dose of study drug through 30 days after the last dose of study drug. All Grade 2-5 AEs as well as special reporting circumstances, such as exposure via a parent during pregnancy or breast-feeding, overdose, medication error, misuse, abuse, off-label use or occupational exposure must be recorded on the CRF.

10.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1. Results in death.
2. Is immediately life-threatening (ie, in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity. (Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.)
5. Is a congenital anomaly or birth defect.

6. Is an important medical event (Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of important medical events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.)

SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs from the date of the first dose of study drug through 30 days following the last dose of study drug, whether or not related to study drug(s), must be recorded on the CRF and must be reported within 2 working days to supporting companies. External sites should report SAEs to the Duke study team within 24 hours. Reporting instructions for external sites can be found in the REDCap study eManual.

All SAEs must be followed until resolution, return to baseline condition, or stabilization. Any SAEs that are ongoing at the time the clinical database is closed will be reported to supporting companies as unresolved.

The initial report for each SAE or death should include at minimum the following information:

- protocol number and title
- patient initials, study identification number, sex, age
- date the event occurred
- description of the event
- seriousness criteria
- event causality or causal relationship
- study drug name(s)
- dose level and cycle number at the time the event occurred
- description of the patient’s condition
- study status of patient at time of report
- responsible investigator name and contact details

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. Whenever possible, the Investigator should also provide the batch or lot number of the study drug(s).

SAE Reporting Procedure:

Immediately upon awareness of a SAE, the Investigator (or designee) completes the **DCI SAE Report Form** and will submit the form within 2 business days of knowledge of the event to the funding companies. External sites should submit the form within 24 hours to the Duke study team via the REDCap SAE reporting tool. In accordance with applicable regulations, Investigators must report SAEs to their local IRB according to their institutional guidelines.

Note: It is imperative that initial SAE reports are submitted as soon as possible (within 2 business days of knowledge of the event) with available information to the supporting companies. Missing and/or clarified event information may be provided in a follow-up report.

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to the supporting company as soon as possible using the same form mentioned above.

The Lead PI will review the report form with accompanying source document, sign page 5 of the form and promptly submit it to the funding companies.

If the event meets the Duke University Health System (DUHS) IRB reporting requirements, the study team regulatory coordinator will submit information about the SAE including the Lead PI's assessment as a safety event to the DUHS IRB within 5 business days. Any study-related death must be reported to the IRB within 24 hours of discovery.

Within two business days of receipt, the study team will submit the SAE report form and other relevant safety information to the following supporting companies:

Merck Global Safety
ATTN: Worldwide Product Safety
[redacted]

Ipsen Safety
ATTN: Ipsen Call Center
[redacted]

Expedited Reporting Procedure for Duke Cancer Institute (Coordinating Center):

Duke Cancer Institute as the coordinating center for this study is responsible for reporting SAEs to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND. If the SAE meets criteria for reporting to the FDA, the study team will complete the Form FDA 3500A (MedWatch) and send to the Lead PI and the supporting companies that are noted above. This submission of the Form FDA 3500A to the FDA attached to the IND will be completed by the Duke GI Oncology Clinical Trials Regulatory Coordinator.

- All unexpected, drug related SAEs that are fatal or life-threatening will be reported to the FDA by phone or fax within 7 calendar days of initial receipt of the information and will provide a complete report within 8 days of the initial report submission (by calendar day 15).

- All unexpected, treatment-related SAEs that are not fatal or life-threatening will be reported in a written report to the FDA within 15 days of initial receipt of the information.

The Duke study team will forward all expedited reports to all participating investigators in the form of an Investigator Alert. The Investigator Alert template is available on the DCI intranet titled "Safey Reporting for Multi-site IITs Notification Email".

10.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI). For the time period beginning with date of first dose of study drug 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, that occurs to any subject must be reported 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.

Events of clinical interest for this trial include:

1. A overdose of pembrolizumab, as defined below in Section 10.3.1, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

10.3.1 Medication Overdose and Error

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 study drug(s), the adverse event(s) is reported as a SAE, even if no other seriousness criteria are met. Refer to SAE reporting procedures in Section 10.2.

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 ECI, using the terminology "accidental or intentional overdose without adverse effect." Refer to ECI reporting procedures.

ECI Reporting Procedure:

Immediately upon awareness of an ECI, the Investigator (or designee) completes the **DCI SAE Report Form** and will submit the form within 2 business days of knowledge of the event to the funding companies. External sites should submit the form within 24 hours to the Duke study team via the REDCap SAE reporting tool.

Note: It is imperative that initial ECI reports are submitted as soon as possible (within 2 business days of knowledge of the event) with available information to the funding companies. Missing and/or clarified event information may be provided in a follow-up report.

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to the funding companies as soon as possible using the same forms mentioned above.

The Lead PI will review the report form with accompanying source document, sign page 5and the PI or designee will then promptly submit it to the funding companies.

Within two business days of receipt, the study team will submit the SAE report form and other relevant safety information to the following supporting companies:

Merck Global Safety
ATTN: Worldwide Product Safety
[redacted]

Ipsen Safety
ATTN: Ipsen Call Center
[redacted]

10.4 Other Safety Considerations

The Investigator must also report in the same timelines as SAEs any incidence of medication error, occupational exposure, abuse or misuse that is associated with or result in an adverse event. All related fatal outcomes must also be reported in the same timeline as a SAE.

Refer to SAE reporting procedures in Section 10.2.

10.4.1 Pregnancy and Lactation

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 funding companies' product, 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.

Such events must be reported according to SAE reporting procedures (refer to Section 10.2).

11.0 ADMINISTRATIVE RESPONSIBILITIES

11.1 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects.

The Investigator should provide the IRB/IEC with reports, updates, and other information (e.g., Safety Updates, Amendment IRB/IECs, and Administrative Letters) according to regulatory requirements and institution procedures.

Copies of all IRB/IEC approvals, as well as annual re-approvals and approved/stamped informed consent forms must be submitted to Duke GI Oncology Clinical Trials Office.

11.2 Protocol and Protocol Revisions

All revisions to the protocol will be provided to the supporting companies by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office. The Lead PI must have written and dated approval/favorable opinion from the Duke University Health System (DUHS) IRB of revised protocol prior to distribution to Investigators at external participating sites.

Investigators must obtain written and dated and approval/favorable opinion from the IRB/IEC before conducting any updated protocol version. Study must be conducted as described in the approved protocol. The Investigator must not implement changes of the approved protocol without prior written agreement by the Lead PI and prior review and documented approval/favorable agreement by the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., changes in research personnel or change in phone numbers).

Documentation of approval(s) from the IRB/IEC must be sent to Duke GI Oncology Clinical Trials Office.

11.3 Protocol Deviations and Violations

A protocol deviation is non-adherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or Good Clinical Practice (GCP) guidelines.

A protocol violation is any significant divergence from the protocol such as non-adherence on the part of the subject, the Investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

As a matter of policy, the Lead PI (ie. sponsor) will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If it is found that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), the Lead PI and/or designee(s) at the Duke GI Oncology Clinical Trials Office must be informed immediately. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the Lead PI and the responsible IRB/IEC.

Protocol deviations and violations must be documented and reported to the Lead PI and/or designee(s) at the Duke GI Oncology Clinical Trials Office.

In accordance with applicable regulations, Investigators must report protocol deviations and violations to their local IRB/IEC according to their institutional guidelines.

11.4 Informed Consent

The Investigator must ensure that subjects or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and their IRB. A copy of the proposed informed consent document must be submitted to the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office for review and comment prior to submission to the local IRB/IEC.

Informed consent must be obtained prior to performing any study-related procedures that are not part of normal subject care, including screening and changes in medications. A copy of the signed informed consent form must be given to the study subject.

11.5 Source and Study Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports (including normal and abnormal results), radiology reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original certified document.

When clinical observations are entered directly into an electronic medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has must be validated to meet the FDA requirements for electronic records and signatures (i.e. meets 21 CFR Part 11 compliant).

Regulations require that Investigators maintain information in the study subject's medical records which corroborate data recorded on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the Lead PI or designee(s), monitors, and/or regulatory inspectors:

- Medical history/physical condition of the study subject prior to involvement in the study sufficient to verify protocol entry criteria.
- Dated note that informed consent was obtained for the subject's participation in the study.
- Dated and signed notes for each subject visit including results of examinations.
- Notations on abnormal lab results and their resolution.
- Dated reports of special assessments (e.g., ECG reports).
- Dated and signed notes regarding adverse events (includng event description, severity, onset date, duration, relation to study treatment, outcome and treatment for adverse event).

- Dated notes regarding concomitant medications taken during the study (including start and stop dates).
- Subject condition upon completion of or withdrawal from the study.

Study documentation includes all CRFs, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed subject consent forms, Statement of Investigator form, and clinical study supplies receipts and distribution records).

The Investigator will prepare and maintain complete and accurate study documentation in compliance with GCP guidelines and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, promptly complete all CRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Lead PI and Duke Cancer Institute (DCI).

The Investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to Lead PI or designee(s) by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Lead PI and DCI or responsible government agencies as required by law.

The Investigator agrees to promptly take any reasonable steps that are requested by the Lead PI or designee(s) as a result of an audit to cure deficiencies in the study documentation and case report forms.

11.6 Case Report Forms

Subject data will be entered (ie. CRFs completed) into an electronic data capture (EDC) system called Medidata RAVE. This database is maintained on a secure Duke University server and is accessible via internet with login and password.

CRFs should be completed by trained study personnel according to guidelines provided by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office. The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. The Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

In the event of discrepant data, the study monitor or study designee will request data clarification from the Investigator or designee for which may be resolved electronically in the EDC system.

Accurate and reliable data collection will be ensured through verification and crosscheck of the CRFs against the Investigator's study records (source document verification) by the study monitor or study designee.

11.7 Monitoring and Audits/Inspections

The study will be monitored both internally by the Lead PI and externally by the Duke Cancer Institute (DCI) Monitoring Team in accordance with their NCI-approved "Institutional Protocol Monitoring Procedures and Guidelines for NIH-sponsored Research Involving Human Subjects".

In terms of internal review, the Lead PI and/or designee(s) will continuously monitor and tabulate adverse events. Appropriate reporting to the DUHS IRB will be made. If an unexpected frequency of Grade 3 or 4 adverse events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The Lead PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled (if applicable);
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately recorded on the CRF in a reasonably timely manner.

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

An external site monitoring plan addendum describes monitoring at participating sites.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

DCI Quality Assurance personnel, or designee, may conduct audits at sites. Audits will include, but not be limited to: audit trail of data handling and processes, SOPs, drug supply, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

Regulatory authorities may also audit an Investigator during or after the study. The Investigator should contact the Lead PI and designee(s) at the Duke GI Oncology Clinical Trials Office as well as their local IRB, immediately if this occurs, and must fully cooperate with governmental (e.g., FDA) audits conducted at a reasonable time in a reasonable manner.

The Duke University Compliance Program - Human Subject Research Compliance (HSRC) section may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The

Lead PI agrees to allow the HSRC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team at the Duke GI Oncology Clinical Trials Office to the CTQA auditor(s) in order to discuss findings and any relevant issues.

11.8 Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all CRFs are complete, and all queries have been resolved) the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office will notify the Investigator of closeout and a study closeout visit will be performed.

The study monitor or study designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include: retention of study files, possibility of site audits, publication policy, and study closure with local IRB.

11.9 Records Retention

The Investigator will maintain the records of study drug disposition, worksheets and all other study-specific documentation (e.g., study files, source documentation) until notified by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office that records may be destroyed. If the application is not filed or is withdrawn, the Investigator will maintain the records for at least two (2) years after the formal discontinuation of the clinical development program for this product(s).

To avoid error, the Investigator will contact the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, the Lead PI or designee(s) will be contacted if the Investigator plans to leave the institution so that arrangements can be made for the transfer of records.

12.0 REFERENCES

1. Vinik AI. Advances in Diagnosis and Treatment of Pancreatic Neuroendocrine Tumors (PNETS). Endocr Pract. 2014 Oct 8:1-23. [Epub ahead of print] PubMed PMID: 25297671.

2. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008 Jun 20;26(18):3063-72.

3. Strosberg JR. Systemic treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETS): current approaches and future options. Endocr Pract. 2014 Feb;20(2):167-75.

4. Sun L, Coy DH. Somatostatin and its Analogs. Curr Drug Targets. 2014 Dec 5.[Epub ahead of print]

5. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009 Oct 1;27(28):4656-63.

6. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruszniewski P; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014 Jul 17;371(3):224-33.

7. Vikman S, Sommaggio R, De La Torre M, Oberg K, Essand M, Giandomenico V, Loskog A, Totterman TH. Midgut carcinoid patients display increased numbers of regulatory T cells in peripheral blood with infiltration into tumor tissue. Acta Oncol. 2009;48(3):391-400.

8. Bhathena SJ, Louie J, Schechter GP et al. Identification of human mononuclear leukocytes bearing receptors for somatostatin and glucagon. Diabetes 1981; 30: 127–131.

9. Faiss S, Pape UF, Böhmig M, Dörffel Y, Mansmann U, Golder W, Riecken EO, Wiedenmann B; International Lanreotide and Interferon Alfa Study Group. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol. 2003 Jul 15;21(14):2689-96.

10. Schultheis AM, Scheel AH, Ozretić L, George J, Thomas RK, Hagemann T, Zander T, Wolf J, Buettner R. PD-L1 expression in small cell neuroendocrine carcinomas. Eur J Cancer. 2015 Jan 9. pii: S0959-8049(14)01166-6.

11. Martín-Richard M, Massutí B, Pineda E, Alonso V, Marmol M, Castellano D, Fonseca E, Galán A, Llanos M, Sala MA, Pericay C, Rivera F, Sastre J, Segura A, Quindós M, Maisonobe P; TTD (Tumores del Tracto Digestivo) Study Group. Antiproliferative effects of lanreotide autogel in patients with progressive, well-differentiated neuroendocrine tumours: a Spanish, multicentre, open-label, single arm phase II study. BMC Cancer. 2013 Sep 20;13:427.

12. Spranger S, et al. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med. 2013; 5:200ra116.10.1126/scitranslmed.3006504

13. Carbognin L, Pilotto S, Milella M, Vaccaro V, Brunelli M, Caliò A, Cuppone F, Sperduti I, Giannarelli D, Chilosi M, Bronte V, Scarpa A, Bria E, Tortora G. Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers. PLoS One. 2015;10(6):e0130142.

Appendix A. RECIST 1.1

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Definitions
Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
- 10mm caliper measurement by clinical exam (when superficial)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Non-measurable Disease
All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors,

where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions
While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions
The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline

lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

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

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

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Appendix B. Immune-Related Response Criteria

The immune related response criteria* (irRC) has been developed to adequately characterize additional patterns of response and progression specific to patients treated with immunotherapy, that cannot be captured by the conventional criteria such as such as Response Evaluation Criteria in Solid Tumors (RECIST).

*Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412–7420.

Antitumor response based on total measurable tumor burden.

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Time-point response assessment using irRC.

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening).

Overall response using the irRC.

The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented
- irPR, decrease in tumor burden ≥50%relative to baseline
  - confirmed by a consecutive assessment at least 4 wk after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

Appendix C. ECOG Performance Status

The ECOG Scale of Performance Status, developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*, describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).

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

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix D. Study Calendar

Study Procedures	Screening Period[1]	Treatment Period[2]		Follow-up Period[3]	
	Days -28 to -1	Day 1 (±7days)	Every 12 Weeks[19]	30 (±7) Days[20]	Long Term
Informed Consent	X[4]				
Demographics	X				
Medical and Cancer History	X				
Concomitant Medications	X	X --- (throughout study)[5] --- X			
Physical Examination	X	X		X	
Height	X				
Vital Signs and Weight[6]	X	X		X	
ECOG Performance Status[7]	X	X		X	
CBC with Differential	X[8]	X[9]		X	
Chemistries including LFTs	X[8]	X[9]		X	
Urinalysis	X[8]	X[9]		X	
Thyroid Function Tests	X		X	X[10]	
Serum Pregnancy Test	X[8]		X	X	
Pembrolizumab[11]		X			
Lanreotide Depot[12]		X			
Adverse Event Assessment	X	X --- (throughout study)[5] --- X			
Tumor Assessment[13]	X		X		X[21]
Chromogranin A	X		X		X[21]
Tumor Tissue	X[14]				
Circulating Immune Cells[15]	X[16]		X[17]	X	
Protein Multiplex Arrays[18]	X[16]		X	X	
Survival					X

1. Refer to Section 5.1.
2. Cycle length is 21 days. For C2 and all subsequent cycles, a window of +/-7 days is allowed for D1 visits. Refer to Section 5.2.
3. Refer to Section 5.3.
4. May be completed more than 28 days prior to Cycle 1 Day 1.
5. Collect this data throughout study when changes or events occur.
6. Temperature (°C), blood pressure, heart rate, and weight (kg).
7. Refer to Appendix C.
8. Must perform within 7 days prior to Cycle 1 Day 1. If completed within 7 days of Cycle 1 Day 1, no need to repeat. If repeated on Cycle 1 Day 1, must wait for results to confirm eligibility prior to starting study drug.
9. After Cycle 1, may perform up to 3 days prior to treatment visit.
10. During follow up period, only performed if clinically indicated.
11. Refer to Section 6.2.
12. Refer to Section 6.3.
13. Radiographic assessments (restaging scans) include CT and/or MRI of chest, abdomen and pelvis every 12 weeks (ie. after every 4 cycles). Same method for tumor assessment should be employed at every assessment.
14. Archived or fresh tumor tissue if available. Refer to Section 8.1 and Study Manual.
15. Peripheral blood. Refer to Section 8.2 and Study Manual.
16. Baseline time point may be obtained on Cycle 1 Day 1 prior to the first dose of study drug.
17. First restaging only (ie. after Cycle 4 only).
18. Peripheral blood. Refer to Section 8.3 and Study Manual.
19. Study procedures for restaging may be completed 12 (±1) weeks.
20. After the last dose of study drug.
21. Subjects discontinued from study treatment with no documented disease progression and no subsequent anti-cancer treatment should have disease status and chromogranin A followed per standard of care schedule until disease progression is documented.

Appendix E. Laboratory Tests

CBC with differential		
• hematocrit • hemoglobin • platelet count	• WBC (total and differential) • red blood cell (RBC) count	• absolute neutrophil count • absolute lymphocyte count
Chemistries with liver function tests (LFTs)		
• albumin • alkaline phosphatase (ALP) • ALT • AST • bicarbonate	• blood urea nitrogen (BUN) • chloride • creatinine • glucose • calcium	• potassium • sodium • total bilirubin • total protein
Urinalysis		
• including blood, glucose, protein, specific gravity		
Thyroid Function Tests		
• thyroid stimulating hormone (TSH)	• total thriiodothyronine (T3)	• free tyroxine (T4)
Pregnancy Test		
• serum β-HCG pregnancy test		