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A PHASE II STUDY OF LENVATINIB, A MULTI-TARGETED TYROSINE KINASE INHIBITOR, COMBINED WITH PEMBROLIZUMAB FOR THE TREATMENT OF METASTATIC GASTROESOPHAGEAL CANCER PATIENTS WHO HAVE PROGRESSED ON FIRST OR SUBSEQUENT LINE THERAPIES

Regulatory Sponsor:	The Laura and Isaac Perlmutter Cancer Center NYU Langone Medical Center 160 E 34th Street New York, NY 10016 (212) 731-5001
Funding Sponsor:	Eisai Inc. (Headquarters) 100 Tice Blvd. Woodcliff Lake, NJ 07677 Telephone: 201-692-1100 Fax: 201-692-1804 Merck Corporate Headquarters 2000 Galloping Hill Road Kenilworth, NJ 07033 U.S.A. Telephone: 908-740-4000
Study Product:	Lenvatinib (Lenvima) Pembrolizumab (Keytruda)
Coordinating Center:	The Laura and Isaac Perlmutter Cancer Center NYU Langone Health
Principal Investigator: **NYU Langone Health**	Paul Oberstein, MD The Laura and Isaac Perlmutter Cancer Center NYU Langone Health 160 East 34th Street New York, NY, 10016 Paul.Oberstein@nyulangone.org
Principal Investigator: **Mount.Sinai Health System**	Deirdre J. Cohen MD The Tisch Cancer Institute Icahn School of Medicine at Mount Sinai 1425 Madison Avenue New York, NY 10029 Deirdre.Cohen@mssm.edu

NYU Protocol Number:	*s17-00626*
NYULH Medical Monitor:	*Stella Lymberis, MD* *NYU Langone Health* *160 East 34th Street* *New York, NY 10016* *Email: Stella.Lymberis@nyulangone.org*
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Version:	January 10, 2020 v1.0 May 18, 2020 v2.0 November 19, 2021 v 3.0

INVESTIGATOR SIGNATURE PAGE

I have read this protocol, including all appendices, and I agree to conduct the study in compliance with all applicable regulations (including 21 CFR Part 312). I will also make a reasonable effort to complete the study within the time designated. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Eisai/Merck. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

I am aware that, prior to the commencement of this study, the Institutional Review Board must approve this protocol and the informed consent document associated with the clinical facility where the study will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol. I agree to provide all subjects with a signed and dated copy of their informed consent document, as required by FDA and ICH regulations. I further agree to report to Eisai/Merck any adverse events in accordance with the terms of this protocol and FDA regulation 21 CFR 312.64.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD/MM/YYYY)

Name of Investigator (please print)

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List of Abbreviations and Definition of Terms

Abbreviation	Explanation
%	Percent
µg	microgram(s)
14C	Carbon-14: radioactive carbon isotope of mass 14, used as a tracer in biochemistry
5-FU	5-Fluorouracil
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
AEOSI	Adverse Event of Significant Interest
aFGF	acidic Fibroblast Growth Factor
AGITG	Australian Gastrointestinal Trials Group
ALK	Anaplastic Lymphoma Kinase (CD 246),
ALT/SGPT	Alanine transaminase or alanine aminotransferase/serum glutamate-pyruvate transaminase, a liver function test
ANC	Absolute Neutrophil Count
AO	Aldehyde Oxidase
aPTT	Activated Partial Thromboplastin Time: a test that characterizes blood coagulation
AST/SGOT	Aspartate transaminase or aspartate aminotransferase/Serum glutamic oxaloacetic transaminase, a liver function test
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
AUCss	Area Under the Curve at steady state
BCG Vaccine	Bacillus Calmette–Guérin vaccine: used primarily against tuberculosis

BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BP	Blood Pressure
BRAF	A human gene that encodes the B-Raf protein, which is involved in directing cell growth.
BSEP	Bile Salt Export Pump
C	Cycle
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CD28	Cluster of Differentiation 28: one of the proteins expressed on T cells that provide co-stimulatory signals required for T cell activation and survival.
CD3	Cluster of Differentiation 3: a T-cell co-receptor that helps to activate the cytotoxic T-Cell.
CD3ζ	CD3zeta or CD247: a T-cell surface glycoprotein and effector molecule involved in the CD3 T-cell signalling cascade important for T-cell activation. Plays an important role in coupling antigen recognition to several intracellular signal-transduction pathways.
CD4	Cluster of Differentiation 4: a glycoprotein found on the surface of immune cells such as T helper cells, monocytes, macrophages, and dendritic cells.
CD8	Cluster of Differentiation 8: a transmembrane glycoprotein that serves as a co-receptor for the T cell receptor.
CDC	Complement-Dependent Cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence Interval
CIN	Chromosomal Instability
CL	Clearance
Cmax	Peak Concentration
Cmin	Trough concentration

CNS	Central Nervous System
CO_2	Carbon Dioxide
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4: a protein receptor that, functioning as an immune checkpoint, downregulates the immune system.
CTO	Clinical Trials Office
CV	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4
D	Day
DCR	Disease Control Rate
Discon.	Discontinuation
dL	Deciliter(s) (10^{-1} Liters)
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DRAE	Drug Related Adverse Event
DTC	Differentiated Thyroid Cancer
EBV	Epstein Barr Virus
EC	Esophageal Cancer
EC50	Effective Concentration
ECG	Electrocardiogram
ECI	Event of Clinical Interest

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
Epo	Erythropoietin
ERC	Ethics Review Committee
ERK1/2	Extracellular signal–regulated kinases 1 and 2
et al.	et alia, a Latin phrase meaning "and others"
Etc.	Et cetera: a Latin expression meaning "and other things", or "and so forth". It is used at the end of a list to indicate that further, similar items are included.
EU	European Union
FDA	The US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FGF	Fibroblast Growth Factor
FGFR1/2/3/4	Fibroblast Growth Factor Receptors 1, 2, 3, and 4
FOXP3	Forkhead box P3, a protein involved in immune system responses and regulation of the development and function of regulatory T cells.
FSH	Follicle Stimulating Hormone
fT4	Free Thyroxine, a thyroid function test
GBM	Glioblastoma, Malignant
GC	Gastric Cancer
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GFR	Glomerular Filtration Rate, a kidney function test

GLP	Good Laboratory Practices
GS	Genomically Stable
GSH	Glutathione
Gy	Gray: a derived unit of ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.
HBsAg	Hepatitis B virus surface antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
hERG	human Ether-à-go-go-Related Gene
HGF	Hepatocyte Growth Factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
Hr	Hour
HUVECS	Human Umbilical Vein Endothelial Cells
i.e.	id est, a Latin phrase meaning “that is”
IB	Investigator's Brochure
IC50	The concentration of an inhibitor required to reduce the rate of an enzymatic reaction by 50%. It is a measure of how effective a drug is.
ICAM1	Intercellular Adhesion Molecule 1
ICH	International Conference on Harmonisation
ICOS	Inducible T Cell Co-stimulator
IEC	Independent Ethics Committee
IFNγ	Interferon Gamma
IgC	Constant immunoglobulin domain

IgG4 κ	Immunoglobulin G4 kappa
IgV	Variable immunoglobulin domain
IHC	Immunohistochemistry
IIR	Independent Imaging Review
IL-2	Interleukin 2: an interleukin, a type of cytokine signaling molecule in the immune system. It is a protein that regulates the activities of white blood cells that are responsible for immunity.
IL-8	Interleukin 8: a chemoattractant cytokine that attracts neutrophils, basophils, and T-cells. It is also involved in neutrophil activation.
IND	Investigational New Drug
INR	International Normalized Ratio: a blood coagulation test
IRB	Institutional Review Board
IRR	Independent Radiologic Review
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IUD	Intrauterine Device
IUO	Investigational Use Only
IV	Intravenous
Kg	Kilogram(s)
KIT	Tyrosine Protein Kinase Kit (CD117)
L	Liter
LMWH	Low Molecular Weight Heparin
M	Meter(s)
mAb	Monoclonal Antibody
MAPK	Mitogen-Activated Protein Kinase
mcL	Microliters (10^{-6} Liter)

MDR	Multi-Drug Resistance Protein
MDSC	Myeloid-Derived Suppressor Cell
MedWatch	The FDA Safety Information and Adverse Event Reporting Program
Mg	Milligram(s) (10^{-3} grams)
Min	Minute
mL	Milliliter(s) (10^{-3} liters)
Mm	Millimeter(s) (10^{-3} meters)
mm/hg	Millimeters of mercury: unit of measure for blood pressure
Mmol	Millimolar (10^{-3} molar)
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
ms	Milliseconds (10^{-3} seconds)
MSI	Microsatellite Instability
MTC	Medullary Thyroid Cancer
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin: a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription
MVD	Microvessel Density
N	Number
NCI	National Cancer Institute
NK	Natural Killer Cells: a type of lymphocyte (white blood cell) and a component of the innate immune system. NK cells play a major role in the host-rejection of both tumors and virally infected cells.
nM or nmol	Nanomolar (10^{-9} molar)
NOAEL	No Observed Adverse Effect Level

NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
NT	Not Tested
NYHA	New York Heart Association
NYU	New York University
NYULH	NYU Langone Health
NYULMC	NYU Langone Medical Center
OAT	Organic Anion Transporter
OATP	Organic Anion Transporter Polypeptide
OOL	Optional Open Label
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over The Counter
PBMCs	Peripheral Blood Mononuclear Cells
PD-1	Programmed cell death protein 1, a cell surface receptor of the immunoglobulin superfamily and expressed on T cells and pro-B cells. It binds two ligands: PD-L1 and PD-L2.
Pdcd1	Gene encoding PD-1
PDGF	Platelet-Derived Growth Factor
PDGFRα	Platelet-Derived Growth Factor Receptor alpha polypeptide
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death Ligand 2
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PHI	Protected Health Information

PK	Pharmacokinetics
PKCθ	Protein Kinase C, an effector molecule involved in the CD3 T-cell signalling cascade important for T-cell activation.
PMDA	Pharmaceutical and Medical Devices Agency
PO	Per os, or by mouth (oral)
PPE	Palmar-Plantar Erythrodysesthesia
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time: a blood coagulation test
PVC	Polyvinylchloride
Q or q	Every
QD	Every Day / Daily
QTc	Corrected QT interval
QTcF	Corrected QT interval according to Fridericia's Correction Formula: A formula which takes into account the physiologic shortening of the QT interval which occurs as the heart rate increases. It is mathematically defined as: QTcF = QT/CubeRootRR(seconds)
RCC	Renal Cell Carcinoma
RECIST v. 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RET	Receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor (GDNF) family of extracellular signalling molecules
RNA	Ribonucleic acid
RPSFT	Rank-Preserving Structural Failure Time
RR	Response Rate
RTK	Receptor Tyrosine Kinase
S6	A ribosomal protein.

S6K	Ribosomal protein S6 kinase: an enzyme and serine/threonine protein kinase. Its target substrate is the S6 ribosomal protein. Phosphorylation of S6 induces protein synthesis at the ribosome. The kinase activity of this protein leads to an increase in protein synthesis and cell proliferation. Amplification of the region of DNA encoding this gene and overexpression of this kinase are seen in some cancer cell lines.
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Stable Disease
SHP-1/2	Src homology region 2 domain-containing phosphatase-1 and 2: tyrosine phosphatases
T/C	Treatment / Control
t1/2	Terminal Half-Life
T1DM	Type 1 Diabetes Mellitus
T3	Total Triiodothyronine, a thyroid function test
TB	Bacillus Tuberculosis
TCGA	The Cancer Genome Atlas
TIL	Tumor Infiltrating Lymphocytes
TK	Toxicokinetic
TKI	Tyrosine Kinase Inhibitor
TNFα	Tumor Necrosis Factor Alpha
TPS	Tumor Proportion Score
Treg	Regulatory T Cell
TSH	Thyroid Stimulating Hormone, a thyroid function test
Tx.	Treatment
ULN	Upper Limit of Normal
US	United States
VCAM1	Vascular cell adhesion protein 1

VEGF	Vascular Endothelial Growth Factor
VEGFR-1 (FLT-1)	Vascular Endothelial Growth Factor Receptor 1 (Fms-Related Tyrosine Kinase 1): a receptor tyrosine kinase that is important for the control of cell proliferation and differentiation.
VEGFR-2 (KDR)	Vascular Endothelial Growth Factor Receptor 2 (Kinase insert domain receptor), a receptor tyrosine kinase that is important for the control of cell proliferation and differentiation.
VEGFR-3 (FLT-4)	Vascular Endothelial Growth Factor Receptor 3 (Fms-related tyrosine kinase 4): a receptor tyrosine kinase that is important for the control of cell proliferation and differentiation.
Vs	Versus
W	Week
ZAP70	Zeta-chain-associated protein kinase 70 is a protein normally expressed near the surface membrane of T cells and natural killer cells. It is part of the T cell receptor, plays a critical role in T-cell signaling, and serves as an effector molecule involved in the CD3 T-cell signalling cascade important for T-cell activation.
β-HCG	Beta Human Chorionic Gonadotropin
µmol/L	Micromolar (10^{-6} molar)

1.0 TRIAL SUMMARY

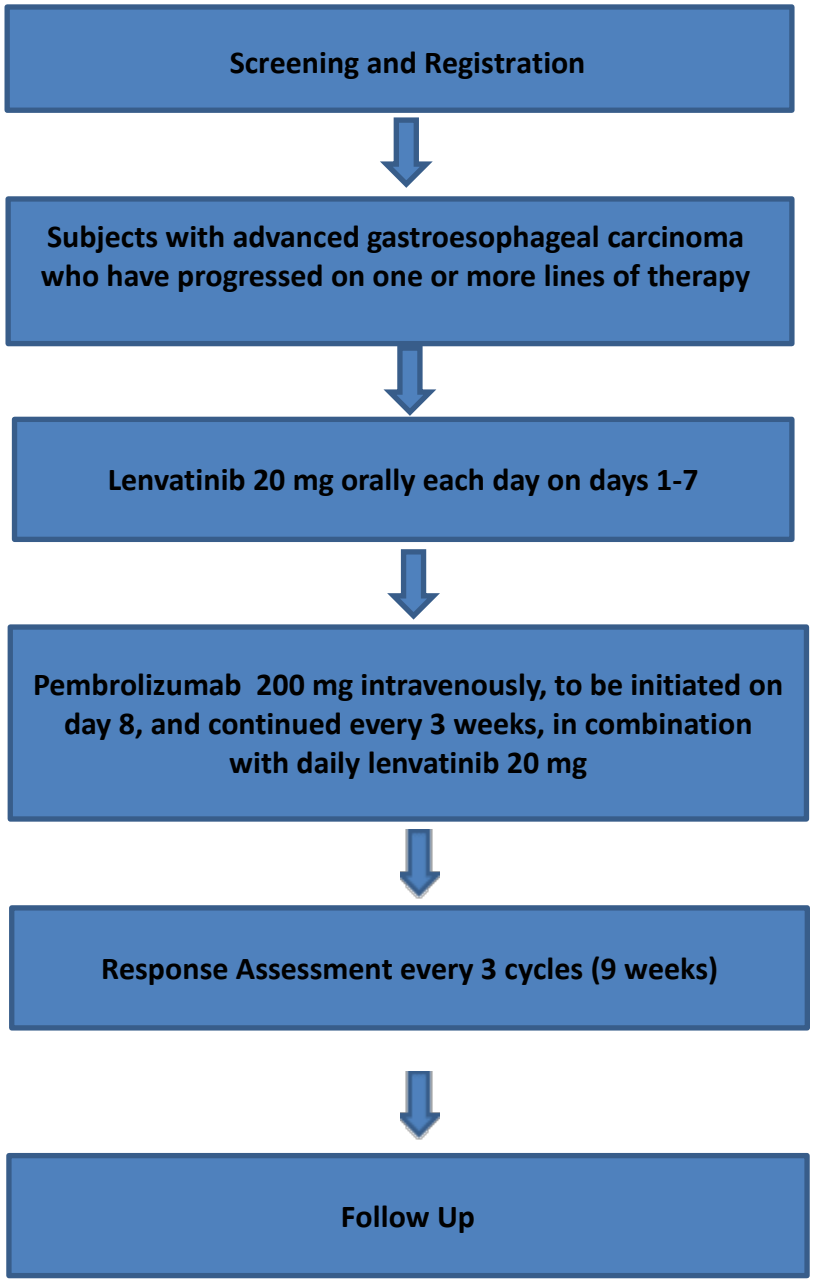
Abbreviated Title	Lenvatinib and pembrolzumab in advanced gastroesophageal cancer
Trial Phase	Phase II
Clinical Indication	Gastric and gastroesophageal junction adenocarcinoma
Trial Type	Single arm
Type of control	n/a
Route of administration	Lenvatinib PO, Pembrolizumab IV
Trial Blinding	n/a
Treatment Groups	n/a
Number of trial subjects	29
Estimated enrollment period	18 months
Estimated duration of trial	30 months
Duration of Participation	8 months
Estimated average length of treatment per subject	6 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open label, single arm, phase II study.

2.2 Trial Diagram - Figure 1



1. **One cycle: 21 days**
2. **Treatment until progression of disease, development of unacceptable toxicity, or at the discretion of the treating physician**
3. **Once off-treatment, subjects will be followed every 12 weeks (+/- 1 week) from the date of last dose of pembrolizumab and/or lenvatinib until death or lost to follow up or until study closure (approximately 6 months after the final subject completes treatment).**

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

Objective:

To determine the overall response rate as measured by RECIST 1.1 for the combination of lenvatinib and pembrolizumab in patients with metastatic gastroesophageal cancer who have progressed on first or subsequent line(s) therapies.

Hypothesis:

Given the significant cross talk between tumor angiogenesis and the immune response, combined therapy with lenvatinib and pembrolizumab in advanced gastroesophageal cancer patients will provide improved outcomes compared to standard treatment with currently approved agents.

3.2 Secondary Objective & Hypothesis

Objective:

To determine the progression free survival (PFS), overall survival (OS), and toxicity rates in advanced gastroesophageal patients treated with lenvatinib and pembrolizumab.

3.3 Exploratory Objective

Objective:

To characterize changes in the immune cell phenotype, immune pathway activity, and immune response following lenvatinib only, and then with the addition of pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Pembrolizumab and Lenvatinib Background

Pemborlizumab and lenvatinib are briefly described below. Refer to the current Investigator's Brochures (IB)/approved labeling for details.

4.1.1 Pembrolizumab 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. 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 been approved in the United Stated for multiple indications including: the treatment of patients with unresectable or metastatic melanoma, patients with metastatic non-small cell lung cancer (NSCLC) previously untreated or who have had disease progression on or after platinum-containing chemotherapy and whose tumor express PD-L1 as determined by an FDA-approved test, patients with recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy, and patients with advanced urothelial carcinoma who are either ineligible or who have progressed on cisplatin-containing chemotherapy. .

4.1.2 Pembrolizumab Preclinical and Clinical Trial Data

4.1.2.1 Nonclinical Pharmacology

Pembrolizumab binds to human and Cynomolgus monkey PD-1 with comparable affinity and blocks the binding of human and Cynomolgus monkey PD-1 to PD-L1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD-1. Pembrolizumab does not bind immunoglobulin superfamily members cluster of differentiation 28 (CD28), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or inducible T-cell costimulator (ICOS).

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and nonhuman primates. In T-cell activation assays using human donor blood cells, the half-maximal effective concentration (EC_{50}) has been approximately 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. In the in vitro peripheral blood mononuclear cell (PBMC) and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low and comparable to those induced by trastuzumab. Pembrolizumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Using anti–murine PD-1 surrogate antibodies, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti–PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU), and combination therapy results in increased complete tumor regression rates in vivo. Studies also revealed that immunosuppressive doses of dexamethasone included in combination with agents used in standard-of-care treatment for NSCLC do not reduce the anti-tumor efficacy of an anti–murine PD-1 surrogate antibody.

4.1.2.2 Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab were evaluated in a non–Good Laboratory Practices (GLP) single dose PK study and two GLP repeat-dose toxicokinetic (TK) studies (1 month and 6 month) in Cynomolgus monkeys. Pembrolizumab stability as a modified IgG4 molecule was evaluated in vivo in mice.

After single-dose IV administration at 0.3, 3, or 30 mg/kg in Cynomolgus monkeys, decline of serum concentration followed multiphasic kinetics. Anti–drug antibodies (ADAs) were detected in most of the treated animals. Clearance (CL) and terminal half-life ($t_{1/2}$) appeared to be dose-dependent in the dose range tested with $t_{1/2}$ varying from 4 to 10 days. In the 1-month repeat-dose (once weekly) GLP toxicity study at 6, 40, or 200 mg/kg in Cynomolgus monkeys, ADAs were detected in most of the low-dose (6 mg/kg) treated animals. The systemic exposure over the 7-day dosing interval ($AUC_{0\text{-}7\ days}$) was sex-independent and increased with increasing dose. The mean $t_{1/2}$ values in individual ADA-negative animals ranged from 15.7 to 22.3 days across doses.

In the 6-month repeat-dose (every other week) GLP toxicity study at 6, 40, or 200 mg/kg in

Cynomolgus monkeys, ADAs were detected in most of the low-dose (6 mg/kg) treated animals. The systemic exposure to pembrolizumab was independent of sex and was approximately dose-proportional across all doses. The mean $t_{1/2}$ values in individual ADA-negative animals ranged from 21 to 22 days across doses.

IgG4 wild type molecule can undergo in vivo molecular rearrangement called Fab-arm (or half molecule) exchange by swapping their half molecule with other IgG4 half molecules, thereby generating bispecific or hybrid antibodies. Pembrolizumab is a hinge mutated IgG4 (S228P), which prevents in vivo half-molecule swap (formation of hybrid). An in vivo mice experiment has demonstrated that pembrolizumab did not form hybrid antibody with another wild type IgG4 molecule.

4.1.2.3 Safety Pharmacology/Toxicology

The potential for systemic toxicity of pembrolizumab was assessed in a 1-month repeat-dose toxicity study with a 4-month recovery in Cynomolgus monkeys and in a 6-month repeat-dose toxicity study with a 4-month recovery period in Cynomolgus monkeys. In the 1-month toxicity study, Cynomolgus monkeys were administered an IV dose of 6, 40, or 200 mg/kg once weekly for a total of 5 doses. Four monkeys/sex/group were euthanized during Week 5. The remaining 2 monkeys/sex/group were euthanized during Week 23, after a 4-month post-dose period. In this study, pembrolizumab was well-tolerated in monkeys with the systemic exposure (AUC) up to approximately 170,000 µg·day/mL over the course of the study. There was no test article–related mortality, and test article–related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving 200 mg/kg. Both of these findings were not considered adverse and there was no histopathologic correlation. Splenic weights were normal at the post-dose necropsy.

Anti–pembrolizumab antibodies were detected in 7 out of 8 animals in the 6 mg/kg dose group and 1 animal out of 8 in the 40 mg/kg dose group and were associated with an apparent increase in clearance of pembrolizumab. The presence of ADA in monkeys in the low-dose group and in 1 monkey in the mid-dose group did not impact the pharmacodynamic response, because sufficient target engagement was demonstrated for the duration of the study (with the exception of 1 low-dose monkey). Additionally, anti–pembrolizumab antibodies were not detected in any monkeys in the high-dose group, suggesting that potential toxicity has been evaluated at the highest exposure levels in the study. Based on the lack of adverse test article–related findings in this study, the no observed adverse effect level (NOAEL) was ≥200 mg/kg.

In the 6-month toxicity study, the potential for systemic toxicity was assessed in Cynomolgus monkeys administered an IV dose of 6, 40, or 200 mg/kg once every other week for approximately 6 months (a total of 12 doses) followed by a 4-month treatment-free period. Three animals/sex/group were designated for interim necropsy at the end of the 6-month dosing phase (3 days after receiving the last dose in Study Week 23); and the remaining monkeys were designated for final necropsy following the 4-month treatment-free period. Pembrolizumab was well tolerated at all dose levels. There were no test article–related ante mortem findings, electrocardiographic or ophthalmic findings, changes at injection sites, gross observations or organ weight changes at the interim or final necropsy. Because there were no test article–related histomorphologic findings at interim necropsy, histomorphologic

evaluation of tissues collected at final necropsy was not conducted. The presence of ADA was observed in 5 out of 10 animals at 6 mg/kg/dose during the dosing phase, which correlated with an apparent increased rate of elimination of pembrolizumab in these animals.
No anti–pembrolizumab antibodies were detected at 40 or 200 mg/kg/dose during the dosing phase, and no pembrolizumab serum concentration profiles in these 2 groups suggested an effect of ADA on pembrolizumab elimination rate. During the treatment-free period, anti–pembrolizumab antibodies were detected in 2 animals at the 6 mg/kg/dose, which already had ADA present during the dosing phase, and in 2 additional animals (1 at the 6 mg/kg/dose and 1 at the 200 mg/kg/dose), which were ADA-negative during the dosing phase. The detection of anti-pembrolizumab antibodies had a minimal effect on the mean group systemic exposure to pembrolizumab during the study and did not impact the evaluation of potential toxicity of pembrolizumab for the duration of the 6-month study, because there were no test article–related effects on any of the parameters examined and no monkey in the mid- and high-dose groups developed ADA during the dosing phase. In conclusion, pembrolizumab administered once every other week over a 6-month duration to Cynomolgus monkeys was well tolerated and the NOAEL was ≥200 mg/kg/dose (the highest dose tested).

In addition, tissue cross-reactivity studies using monkey and human specimens were conducted to evaluate the potential cross reactivity of pembrolizumab with cryosections of Cynomolgus monkey tissues and normal human tissues. Results demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. The off-target staining (cytoplasmic and stromal) that occurred in many tissues of both species was considered spurious binding inherent to the experimental conditions of the in vitro tissue cross-reactivity studies with no in vivo toxicological significance.

4.1.2.4 Clinical Summary of Results

As of the data cutoff dates for the IB (dated 17-FEB-2017) pembrolizumab monotherapy and combination therapies have been administered to approximately 9833 subjects with hematologic malignancies and solid tumors in Merck-sponsored trials

4.1.2.5 Clinical Pharmacology

The pharmacokinetic 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 200mg). Furthermore, pembrolizumab has a low potential of eliciting the formation of anti-drug antibodies.

The pharmacokinetics of pembrolizumab was studied in 2195 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on population pharmacokinetic analyses in patients with solid tumors, the geometric mean [% coefficient of variation (CV%)] for clearance, steady state volume of distribution, and terminal half-life were 202 mL/day (37%), 7.38 L (19%) and 27 days (38%), respectively.

Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration

versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

4.1.2.6 Safety

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications, 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 (0.4%).
Furthermore, the frequency of immune-mediated 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.
In the pembrolizumab monotherapy trials (P001/P002, P012, P013, and P028, plus the P011 monotherapy arm), the overall incidence of AEs ranged from 83.0% (73 of 88 subjects in P012) to 100% (10 of 10 subjects in P011). The most commonly reported AEs included fatigue, diarrhea, decreased appetite, nausea, and anemia. The incidence of drug -related AEs (DRAEs) ranged from 39.8% (35 of 88 subjects in P013) to 80.0% (8 of 10 subjects in P011). The most commonly reported DRAEs across all studies were nausea, fatigue, and diarrhea. The incidence of Grade 3-5 DRAEs across studies ranged from 6.8% (6 of 88 in P013) to 12.0% (187 of 1562 subjects) in P001/P002. The most commonly reported Grade 3-5 DRAEs were anemia, increased alanine aminotransferase, and increased aspartate aminotransferase . Most subjects who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 1.9% (8 of 430 subjects in P028) to 12.3% (192 of 1562 subjects in P001/P002). The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a DRAE were infrequent and ranged from 0% (no subjects in P011) to 4.5% (4 of 88 subjects in P013). The most commonly reported DRAEs leading to discontinuation were pneumonitis, alanine increased aminotransferase, and increased aspartate aminotransferase.

The overall pattern of AEs observed in melanoma subjects enrolled in P002 demonstrates favorable safety profile when this immune therapy is compared to chemotherapy. Consistent with prior observations from randomized comparisons of the 2 mg/kg and 10 mg/kg dose levels when given every 3 weeks, there are no important differences in the safety profile of pembrolizumab at these 2 dose levels, and both doses appear to have a favorable safety profile compared to chemotherapy.

In the combination therapy trials (P021 and P023), the overall incidence of AEs was 95.4% (62 of 65 subjects) in P021 and 80% (8 of 10 subjects) in P023. In P021, the most commonly reported AEs in this population across the dose regimens were fatigue (49.2%), constipation and nausea (26.2% each), decreased appetite (23.1%), diarrhea (18.5%), and anemia and alopecia (15.4% each). In P023, the most commonly reported AEs experienced in this population across the dose regimens were neutropenia and thrombocytopenia (50.0% each), followed by anemia, respiratory tract infection, and back pain (30.0% each). The incidence of DRAEs was 86.2% (56 of 65 subjects in this population) in P021 and 60.0% (6 of 10 subjects in this population) in P023. In P021, the most commonly reported DRAEs experienced in this population across the dose regimens are fatigue (35.4%); nausea, decreased appetite, and alopecia (13.8% each); diarrhea (12.3%); and constipation and aspartate aminotransferase increased (10.8% each). In P023, the most commonly reported DRAEs experienced in this

population across the dose regimens were neutropenia and thrombocytopenia (50.0% each), anemia (30.0%), dysphonia, hiccups, and pruritis (20.0% each).

Grade 3-5 DRAEs were reported in 23.1% (15 of 65 subjects in this population) in P021 and 50.0% (5 of 10 subjects in this population) in P023. In P021, the most common Grade 3-5 DRAEs in this population across dose regimens were aspartate aminotransferase increased (6.2%) and anemia and alanine aminotransferase increased (4.6% each). In P023, the only Grade 3-5 DRAEs that occurred in more than 1 subject in this population across dose regimens were neutropenia (40.0%) and anemia (20.0%).

In P021, most subjects continued treatment despite AEs, and only 4.6% discontinued due to an AE. Only 3.1% of subjects discontinued study treatment due to an AE that was considered related to study treatment by Investigators. Adverse events resulting in discontinuation were reported in 3.1% (2 of 65 subjects). Interstitial lung disease, dermatitis allergic, and drug eruption were the only AEs resulting in discontinuation and were reported in 1 subject each (1.5%). In P023, no subjects discontinued due to an AE.

In general, the incidence of drug-related serious adverse events (DRSAEs) was low. Many of the events occurred in 1 subject each and/or <1.0% each.

In the pembrolizumab monotherapy trials, the most commonly reported DRSAEs (those that occurred in 3 or more subjects overall in at least 1 study) were pneumonitis (range of 0.7% to 1.3% of subjects); colitis (range of 0.3% to 0.9% of subjects), pyrexia (range of 0.3% to 0.5% of subjects); diarrhea (range of 0.2% to 0.4%); hepatitis (0.7% of subjects); nausea, adrenal insufficiency, hyponatraemia, hyperthyroidism, hypophysitis, vomiting, and dyspnea (0.3% of subjects each); and dehydration, generalized edema, hypothyroidism, renal failure acute, and pericardial effusion (0.2% of subjects each). The remaining DRSAEs occurred in 1 or 2 subjects each per study.

In the combination therapy trials, all DRSAEs were reported in 1 subject each. In P021, 8 subjects experienced DRSAEs; the DRSAEs were as follows: anemia, febrile neutropenia, atrial fibrillation, colitis, pyrexia, hypersensitivity, alanine aminotransferase increased, aspartate aminotransferase increased, drug eruption, rash, and urticaria. In P023, 2 subjects experienced DRSAEs; 1 subject had an event of pneumonia and the other had an event of tumor lysis syndrome.

Due to the fact that P021 and P023 were combination studies, and also because of the small sample size, comparative evaluation of the AE profile of pembrolizumab combination therapy from those protocols to pembrolizumab monotherapy or to chemotherapy monotherapy in other studies cannot be made.

Among P001 and P002 studies, the incidence of Adverse Events of Significant Interest (AEOSI) was 16.1%. Overall, the most commonly reported AEOSI included hypothyroidism (7.2% of subjects), pneumonitis (2.9% of subjects), infusion reaction (2.5% of subjects), and hyperthyroidism (2.2% of subjects). The incidences of the remaining AEOSI were low (range of 0.1 to 1.3% of subjects). The overall incidence of drug-related AEOSI was 14.3%. Overall,

2.6% of subjects discontinued treatment due to an AEOSI and the most commonly reported drug-related.

AEOSI leading to discontinuation was pneumonitis (1.3% of subjects). Only one subject died of AEOSI (pneumonitis, 0.1% of subjects). No corticosteroids were used to manage myositis, pericarditis, thyroiditis, type 1 diabetes mellitus, uveitis and vasculitis.

4.1.2.7 Clinical Efficacy: Melanoma

The safety and efficacy of pembrolizumab were evaluated in a randomized (1:1:1), open-label, multicenter, active-controlled trial in patients with ipilimumab-naive melanoma Patients were randomized to receive pembrolizumab at a dose of 10 mg/kg every 2 weeks or 10mg/kg every 3 weeks as an intravenous infusion until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs.1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS), as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration.

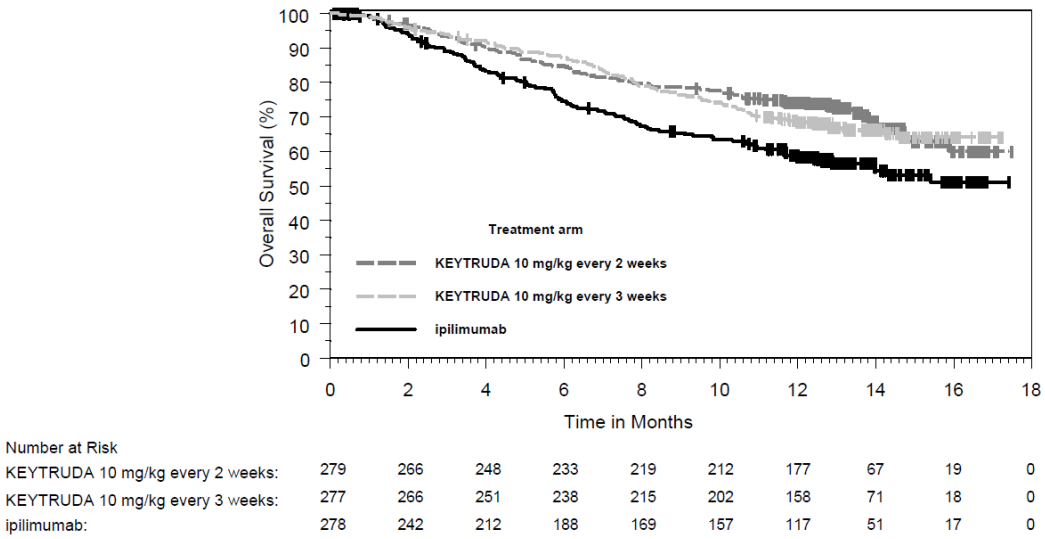
A total of 834 patients were randomized: 277 patients to the pembrolizumab 10 mg/kg every 3 weeks arm, 279 to the pembrolizumab 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study demonstrated statistically significant improvements in OS and PFS for patients randomized to pembolizumab as compared to ipilimumab (see below, Table 1 and Figure 1).

Table 1: Efficacy results

	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab 3 mg/kg every 3 weeks n=278
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best overall response by BICR			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%

* Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

Figure 2: Kaplan-Meier Curve for Overall Survival



Number at Risk

KEYTRUDA 10 mg/kg every 2 weeks:	279	266	248	233	219	212	177	67	19	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	266	251	238	215	202	158	71	18	0
ipilimumab:	278	242	212	188	169	157	117	51	17	0

4.1.2.8 Clinical Efficacy: Non-Small Cell Lung Cancer (NSCLC)

The efficacy of pembrolizumab was investigated in a sub-group of a cohort of 280 patients enrolled in a multicenter, open-label multi-cohort, activity-estimating study. The cohort consisted of patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay. Patients

with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

A prospectively defined sub-group was retrospectively analyzed using an analytically validated test for PD-L1 expression tumor proportion score (TPS). This retrospectively identified sub-group of 61 patients accounts for 22% of the 280 patients in the cohort. Patients included in this sub-group had a PD-L1 expression TPS of greater than or equal to 50% tumor cells as determined by the PD-L1 IHC 22C3 pharmDx Kit. Patients received KEYTRUDA 10 mg/kg every 2 (n=27) or 3 (n=34) weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1 as assessed by BICR and duration of response.

Among the 61 patients with a TPS greater than or equal to 50%, the baseline characteristics were:

median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG PS 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (75%); M1 (98%); brain metastases (11%); one (26%), two (30%), or three or more (44%) prior therapies; and the incidence of genomic aberrations was EGFR (10%) or ALK (0%).

Efficacy results are summarized in Table 2. The ORR and duration of response were similar regardless of schedule (every 2 weeks or every 3 weeks) and thus the data below are pooled.

Table 2: Efficacy Results

Endpoint	n=61
Overall Response Rate	
ORR %, (95% CI)	41% (29, 54)
Complete Response	0%
Partial Response	41%

4.1.3 Lenvatinib Pharmaceutical and Therapeutic Background

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. Many molecules have been implicated as positive regulators of angiogenesis including vascular endothelial growth factor (VEGF), acidic fibroblast growth factor (aFGF), basic FGF, hepatocyte growth factor (HGF), interleukin (IL)-8, and platelet-derived growth factor (PDGF).

Of the numerous molecules that have been shown to have angiogenic properties, VEGF has been identified as a crucial regulator of both physiologic and pathologic angiogenesis with increased expression being associated with a poor prognosis in many human tumor types, including gastroesophageal cancers. VEGF acts primarily on endothelial cells to promote their

proliferation and three-dimensional organization for tube formation and is thought to be the most potent and specific proangiogenic factor. VEGF exerts its effects through two cell membrane bound receptors, VEGFR1 and 2, of which VEGFR2 is thought to be more important. There is substantial evidence that VEGFR2 is the major mediator of endothelial cell proliferation and survival as well as tube formation and microvascular permeability. VEGFR2 undergoes dimerization and ligand-dependent tyrosine phosphorylation, producing a mitogenic, chemotactic and pro-survival signal. An inhibitor of VEGFR2 would therefore be expected to exert a potent inhibitory effect on tumor growth and metastasis formation.

Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of VEGF receptors VEGFR1, VEGFR2, and VEGFR3. Lenvatinib also inhibits other receptor tyrosine kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions. These include FGF receptors FGFR1, 2, 3, and 4; PDGFRα, KIT, and RET. Lenvatinib interacts with VEGFR2 with a novel binding mode recently categorized as Type V resulting in high selectivity, rapid association kinetics and relatively slow dissociation kinetics for the target.[1] Lenvatinib binds to the adenosine triphosphate (ATP)-binding site and the neighboring allosteric region in the kinase domain adopting the aspartic acid-phenylalanine-glycine (DFG)-in conformation. This results in superior binding affinity of lenvatinib to VEGFR2. Most of the known receptor tyrosine kinase inhibitors are categorized as: 1) Type I inhibitors which bind the kinase in the DFG-in configuration and only bind to the ATP-binding site; or 2) Type II inhibitors which bind the kinase in the DFG-out conformation and bind to both the ATP-binding site and the neighboring regions.

The results of in vitro receptor binding assays, cell-based assays, and an in vivo angiogenesis models as well as the results of recent studies in human xenograft models in athymic mice suggest that in most tumors, the mode of action for lenvatinib antitumor activity is primarily related to the inhibition of both VEGF and FGF-dependent angiogenesis.[2, 3] Specifically, intracellular signal transduction analysis for MAPK/Erk1/2, S6K, S6, and their phosphorylated forms in HUVECs revealed that lenvatinib inhibited the MAPK pathway and the mTOR-S6K-S6 pathway triggered by activated VEGFR and FGFR, both of which are important intracellular signaling pathways for angiogenesis. Since cross talk between the VEGF signaling pathway and the FGF signaling pathway may accelerate angiogenesis in the tumor, this mode of dual inhibition may more effectively inhibit tumor angiogenesis. In addition, recent data from preclinical studies suggest that the FGFR pathway is also a driver resistance to antiangiogenic drugs.[4] Lenvatinib targets both VEGFR- and FGFR-induced angiogenesis thereby blocking this mechanism of tumor resistance.

Lenvatinib has been approved in the US for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

4.1.4 Lenvatinib Preclinical and Clinical Trial Data

4.1.4.1 Nonclinical Pharmacology

A cell free kinase inhibition profiling study revealed that lenvatinib is a potent multiple tyrosine kinase inhibitor. The most sensitive kinases with half-maximal inhibitory

concentration (IC_{50}) values below 10 nmol/L include VEGF receptors (VEGFR1, VEGFR2, VEGFR3) and RET. The second most sensitive group includes FGF receptors (FGFR1 - 4), PDGFRα, and KIT with IC_{50} values below 100 nmol/L. All are typical pro-angiogenic and oncogenic pathway-related receptor tyrosine kinases.

Table 3: Kinase IC_{50} Values

Kinase	IC_{50} (nmol/L)
VEGFR3 (FLT4)	2.3
VEGFR2 (KDR)	3.0
VEGFR1 (FLT1)	4.6
RET	6.4
FGFR2	27
PDGFRα	29
FGFR4	43
FGFR3	52
FGFR1	61
KIT	85

FGFR= Fibroblast Growth Factor Receptor
IC_{50} = with half-maximal Inhibitory Concentration
PDGFRα = Platelet-Derived Growth Factor Receptor alpha
VEGFR = Vascular Endothelial Growth Factor

In cell-based assays, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation, proliferation, and tube formation in human umbilical vein endothelial cell (HUVEC) models with IC50 values of 0.25, 3.4, and 2.1 nmol/L, respectively. Lenvatinib also inhibited FGF-driven HUVEC tube formation of with an IC50 value of 7.3 nmol/L. These results indicated that lenvatinib inhibits both VEGF- and FGF-driven angiogenesis in vitro.

In human tumor xenograft models in athymic mice, orally administered lenvatinib (administered as lenvatinib mesylate) significantly inhibited the growth of many different tumors at doses between 1 and 100 mg/kg (see Table 4).

Table 4: Summary of the Anti-Tumor Effects of Lenvatinib Monotherapy

Tumor	Schedule	Lenvatinib dose (mg/kg)[a]				
		1	3	10	30	100
		T/C (%)				
K1 papillary thyroid carcinoma	QDx14	80	71	51	28	13
		70	61	54	30	16
RO82-W-1 follicular thyroid carcinoma	QDx21	63	59	42	34	20
8305C anaplastic thyroid carcinoma	QDx14	68	61	42	30	21
SW579 thyroid-derived squamous cell carcinoma	QDx14	NT	-1	-18	-20	-23
TT medullary thyroid carcinoma	QDx28	NT	NT	16	5	-6
PLC/PRF/5 hepatocellular carcinoma	QDx14	62	44	29	16	6
		63	54	29	14	16
H460 non-small cell lung cancer	QDx14	73	72	55	29	12
Colo205 colorectal cancer	QDx11	50	45	26	13	4
A375 melanoma	QDx14	NT	61	43	29	NT
		NT	NT	26[b]	NT	NT
A549 non-small cell lung cancer	QDx28	NT	13	9	2	NT
MKN-74 gastric cancer	QDx28	NT	34	14	10	NT
SEKI melanoma	QDx17	NT	NT	66	NT	NT
KP-4 pancreatic cancer	QDx17	NT	NT	53	NT	NT
IM95 gastric cancer	QDx21	NT	NT	23	NT	NT
A2780 ovarian cancer	QDx8	NT	NT	50	NT	NT
A-498 RCC	QDx14	NT	NT	26	NT	NT
Caki-1 RCC	QDx14	NT	NT	2	NT	NT
KP-1/VEGF recombinant	QDx14	NT	57[c]	24	NT	NT
KP-1/FGF recombinant	QDx10	NT	68[c]	51	NT	NT

Antitumor effect is shown as T/C (%), where T and C are the change of tumor volume after Day 1 of dosing in the treatment and control groups, respectively.
NT = not tested, QD = once a day, T/C = treatment/control.
a: Dose expressed in terms of mesylate salt.
b: At a dose of 15 mg/kg.
c: At a dose of 7.5 mg/kg.

4.1.4.2 Nonclinical Pharmacokinetics

The PK of lenvatinib in mice, rats, dogs, and monkeys were characterized by a low plasma clearance and a small to moderate volume of distribution. After oral administration of lenvatinib at 3 mg/kg as a solution, lenvatinib was absorbed rapidly and exhibited good oral bioavailability in mice (64.4%), rats (68.7%), dogs (70.4%), and monkeys (78.4%).

In vitro plasma protein binding of lenvatinib (0.3 – 30 µg/mL) was highest in humans (97.87% – 98.62%), followed by rats, athymic mice, monkeys, and dogs. In humans, lenvatinib mainly bound to albumin. In vitro blood to plasma ratios of lenvatinib (0.1 - 10 µg/mL) remained constant in humans (0.589 – 0.608); in contrast, the ratios in animals were lower with increasing concentration.

In human liver microsomes, the demethylated form of lenvatinib was identified as the major metabolite. This metabolite was also detected after incubation with mouse, rat, dog, and monkey liver microsomes. Cytochrome P450 (CYP)3A4 was the predominant (>80%) CYP isoform involved in the metabolism of lenvatinib. Aldehyde oxidase (AO) in human liver 9000×g supernatant of homogenate (S9) generated M3′ from lenvatinib and M2′ from M2. About 50 metabolites were detected in plasma, tissues, urine, feces, and bile samples after a single oral administration of [14C]lenvatinib (radiolabeled on the quinoline ring) to rats and

monkeys at 3 mg/kg. More than 50% of methanol extractable radioactivity in plasma was parent drug, lenvatinib, and oxidative metabolism was one of the main metabolic pathways of lenvatinib. In addition to oxidative metabolism, glutathione (GSH) conjugation with elimination of the O-aryl group followed by further biotransformations (hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates and subsequent dimerization) were the major metabolic pathways after [14C]lenvatinib administration. Cleavage of the O-aryl bond followed by further biotransformations (conjugate with glucuronic acid, glutathione, and N-acetyl glucosamine with or without hydroxylation) were the major metabolic pathways after [14C]CB-lenvatinib (radiolabeled on the chlorobenzene ring). In human plasma, lenvatinib and its metabolite, the N-cysteine conjugate of the quinoline moiety in lenvatinib, could form covalent bonds with human plasma protein(s) via the thioether and disulfide bonds, respectively. Nucleophiles such as GSH and cysteine successfully released lenvatinib-related components which covalently bound to human plasma protein as the corresponding conjugates via a substitution reaction, suggesting that the covalent binding would be reversible in humans in vivo.

After a single oral administration of [14C]lenvatinib (3 mg/kg) to rats and monkeys, radioactivity was mainly excreted in feces, and 90% or more of the radioactive dose was recovered by 7 days post-dose. In rats, oral absorption of radioactivity was at least 65%, which coincided with oral bioavailability of lenvatinib. Tissue distribution and elimination of radioactivity in most tissues were parallel with that in blood or plasma in rats and monkeys, while the elimination of radioactivity in the melanin-containing tissues was slow in monkeys.

The placental transfer of lenvatinib after a single oral administration of [14C]lenvatinib (3 mg/kg) to pregnant rats was very low in rats on Days 13 and 18 of pregnancy. The radioactivity in milk was approximately 2 times higher than that in plasma after a single oral administration of [14C]lenvatinib mesylate to lactating rats (3 mg/kg), and the radioactivity in the milk decreased in parallel with that in plasma. Radioactivity detected in the milk and plasma was primarily attributed to the parent drug, lenvatinib.

Lenvatinib exhibited a potent inhibitory effect on CYP2C8 (IC50: 10.1 μmol/L), a weak inhibitory effect on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A and virtually no inhibitory effect on CYP2A6 and CYP2E1 in human liver microsomes. Time-dependent inhibition by lenvatinib of the formation of 1'-hydroxymidazolam from midazolam (CYP3A4) was observed. The results of the simulations using Simcyp® suggested that there is no significant drug-drug interaction risk between lenvatinib and midazolam (CYP3A substrate) or repaglinide (CYP2C8 substrate) at the clinical dose of 24 mg of lenvatinib.

Treatment of cultured human hepatocytes with up to 3 μmol/L of lenvatinib had a tendency towards a slight increase in CYP3A enzyme activity or CYP3A4 mRNA expression. No effects on CYP1A1, CYP1A2, CYP2C9, and CYP2B6 based on enzyme activities or messenger (mRNA) expression.

In human liver microsomes, lenvatinib directly inhibited 5′-diphospho-glucuronosyltransferase (UGT)1A1 and UGT1A4 with IC50 values of 10.6 and 14.0 μmol/L,

respectively. Lenvatinib showed no or little evidence of direct inhibition of UGT1A6, UGT1A9, and UGT2B7 (IC50 values greater than 30.0 µmol/L). Treatment of cultured human hepatocytes with up to 3 µmol/L of lenvatinib did not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 enzyme activities or mRNA expression.

Lenvatinib was a substrate for multidrug resistance protein 1 (MDR1, = P-glycoprotein [P-gp]) and breast cancer resistance protein (BCRP) and showed inhibitory activity toward P-gp-mediated and BCRP-mediated transports (IC50>30 µmol/L). Lenvatinib was not a substrate for organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, or bile salt export pump (BSEP). Lenvatinib showed an inhibitory effect on OAT1, OAT3, OCT1, OCT2, OATP1B1, and BSEP with the IC50 values of 4 to 15 µmol/L, and no inhibitory effect on OATP1B3 (IC50 >30 µmol/L). Treatment of cultured human hepatocytes with up to 3 µmol/L of lenvatinib showed no induction potency on P-gp mRNA expression. In human liver cytosol, lenvatinib did not inhibit AO activity (IC50 >100 µmol/L).

4.1.4.3 Safety Pharmacology/Toxicology

In the chronic toxicity studies in rats and cynomolgus monkeys, target organ toxicity was primarily observed in the kidneys (glomerulopathy, sometimes with proteinuria), gastrointestinal tract (duodenal lesions), artery/arterioles (arterial fibrinoid necrosis, medial degeneration, or hemorrhage) in various organs, bone (increased epiphyseal growth plate/cartilage), and male and female reproductive organs (testicular hypocellularity and ovarian follicular atresia and decreased menstruation [monkeys]) in both species, and in the incisor (dysplasia) and adrenals (sinusoidal dilatation, cortical necrosis) in rats. All of these findings were not unexpected as similar findings have been reported in animals treated with other TKIs and are considered to be related to the pharmacologic (antiangiogenic) effects of lenvatinib. These findings were reversible and most were not evident at the end of the 4-week recovery period.

The effects of lenvatinib on the cardiovascular, respiratory, and central nervous system (CNS) were evaluated in rats and dogs. Two in vitro electrophysiology studies were also conducted to assess the effect of lenvatinib on human ether-à-go-go-related gene (hERG) potassium current or action potential parameters. No significant adverse effects were observed in these studies except for a weak inhibitory effect on hERG potassium current (IC50 = 11.89 µmol/L).

In view of these results, lenvatinib is anticipated to have a low risk of cardiovascular, respiratory, and CNS adverse effects in humans. However, hypertension is an identified clinical risk associated with clinical use of lenvatinib and other VEGF inhibitors.

4.1.4.4 Clinical Summary of Results

As of the data cutoff date of 27 Apr 2015, a total of 31 clinical studies in the Clinical Development Program have enrolled subjects. Of these 31 studies, 22 are completed (14 Phase 1/1b, 7 Phase 2, and 1 Phase 3), 8 are ongoing (1 Phase 1, 5 Phase 2, 1 Phase 3, and 1 Expanded Access Program), and 1 was discontinued.

4.1.4.5 Clinical Pharmacology

Data from the clinical pharmacology studies showed lenvatinib:
• Exhibits linear PK and minimal accumulation at clinically relevant doses
• Is extensively metabolized with no major metabolites
• Has an elimination half-life of approximately 28 hours
• Has no clinically significant drug-drug interactions
• Has no food effect
• Does not prolong QTc interval in healthy volunteers (increases >10 msec excluded)

Absorption: After oral administration of lenvatinib, time to peak plasma concentration (Tmax) typically occurs from 1 to 4 hours post-dose. Administration with food does not affect the extent of absorption, but decreases the rate of absorption and delays the median Tmax from 2 hours to 4 hours.

In patients with solid tumors administered single and multiple doses of lenvatinib once daily, the maximum lenvatinib plasma concentration (Cmax) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution: In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL).

Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP).

Elimination: Plasma concentrations declined bi-exponentially following Cmax. The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism: CYP3A is one of the main metabolic enzymes of lenvatinib. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion: Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

4.1.4.6 Safety

Safety data obtained in 1,108 patients with advanced solid tumors who received lenvatinib as a single agent across multiple clinical studies was used to further characterize risks of serious adverse drug reactions.

The most common adverse reactions observed in lenvatinib-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving lenvatinib and 5% of patients receiving placebo; 18% of patients discontinued lenvatinib and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of lenvatinib were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of lenvatinib were hypertension (1%) and asthenia (1%)

4.1.4.7 Clinical Efficacy

4.1.4.7.1 Phase I /Ib studies

There were a total of 34 confirmed PRs observed in four studies across all doses as of the cutoff date of 27 Apr 2014, including 7 (20.6%) in Study E7080-E044-101, 10 (29.4%) in Study E7080-A001-102 (Schedules 1 and 2), 1 (2.9%) in Study E7080-J081-103, and 16 (47.1%) in Study E7080-J081-110. One CR was observed in Study E7080-J081-110.

Study E7080-J081-110 is completed. Objective response rate (ORR [CR + PR]) was 60.7% (17 of 28 subjects) overall, 68.2% (15 of 22 subjects) in the combined 4 mg BID group (dose-escalation cohort and expansion cohort combined), and 33.3% (2 of 6 subjects) in the 6 mg BID group.

4.1.4.7.2 Phase II studies

There were a total of 13 Phase 2 studies: 7 are completed, 5 are ongoing, and 1 was closed to enrollment. Of the 7 completed studies, 2 were conducted in subjects with melanoma (E7080-G000-206, E7080-702), one was in DTC and medullary thyroid cancer (MTC) (E7080-G000-201), one in Advanced Hepatocellular Carcinoma (HCC) (E7080-J081-202), one in recurrent Grade 3 or 4 GBM (glioblastoma, malignant) (E7080-G000-203), and one in advanced endometrial cancer (E7080-G000-204), and one in ATC or DTC or MTC (E7080-J081-208]). Study E7080-701 was conducted in ovarian cancer and was closed to enrollment. Completed studies are those for which enrollment has been completed and the primary analysis has been conducted. In some cases, subjects will continue to receive treatment if they are receiving clinical benefit.

Study E7080-G000-203 showed modest antitumor activity and no clinical or OS advantage for lenvatinib over bevacizumab in subject with Grade 4 GBM. PFS and OS results showed no difference in these outcomes between recurrent Grade 4 GBM subjects treated with lenvatinib and those treated with bevacizumab (Cohort 1). Although OS rates at 12 and 18 months were numerically higher in the lenvatinib than in the bevacizumab arm (lenvatinib 37% and 24% vs bevacizumab 22% and 9%), in the context of a PFS-6 of 21.2%, median OS of only 7.5 months

for lenvatinib, and the difference in median OS of only 1.5 months between lenvatinib and bevacizumab, the DMC and Eisai concurred that lenvatinib does not provide additional benefit over bevacizumab in these subjects. The activity of lenvatinib was limited in subjects with recurrent Grade 3 GBM (Cohort 2), with a 6-month PFS rate of 8.0%, median PFS of 2.8 months, and median OS of 12.0 months (median 17.7 months of follow-up). The activity of lenvatinib was unimpressive in subjects with recurrent Grade 4 GBM who failed prior bevacizumab therapy (Cohort 3), with a 6-month PFS rate of 7.6%, median PFS of 1.8 months, and median OS of 4.1 months (median 23.4 months of follow-up) in these subjects.

In Study E7080-G000-204, treatment with lenvatinib resulted in antitumor activity in subjects with recurrent metastatic endometrial cancer with evidence of disease progression following platinum-based chemotherapy. The primary endpoint of the study was the ORR; 19 (14.3%) subjects achieved a best overall response of CR (1 subject) or PR (18 subjects) based on the assessments by the independent radiologic review (IRR), and 28 (21.1%) subjects achieved CR (2 subjects) or PR (26 subjects) based on investigator assessments in the Full Analyses Set. Results from the Per Protocol Analysis Set were similar, with an ORR of 15.7% (19 subjects) based on the assessments by the IRR and 22.3% (27 subjects) based on investigator assessments, indicating that lenvatinib is active as a second-line treatment in subjects with advanced endometrial cancer. Median OS was 9.6 months (median follow-up was 9.6 months). The median OS increased to 10.6 months based on an updated survival assessment at 59.4% of events and a median follow-up at 15.2 months that took place approximately 6 months later. The median estimate of PFS was 5.6 months based on IRR assessment. The 3- and 6-month PFS rates were 66.1% and 41.0%, respectively, based on IRR assessment.

Study E7080-G000-206 primary objective was to assess the objective response rate (ORR; complete response + partial response [CR + PR]) of lenvatinib in subjects with unresectable Stage III or Stage IV melanoma not harboring the V600E BRAF mutation and disease progression following up to 2 prior systemic anticancer regimens for unresectable Stage III or Stage IV melanoma (Cohort 1) and in in subjects with unresectable Stage III or Stage IV melanoma harboring the activating BRAF mutations (mainly the V600E mutation) and disease progression following BRAF V600E-targeted therapy (Cohort 2). The ORR was similar for both subjects with or without the V600 E BRAF mutation. The ORR was 8.6% (8 subjects) in Cohort 1 and 9.0% (8 subjects) in Cohort 2. All were partial responses. Treatment with lenvatinib resulted in some antitumor activity in subjects with unresectable Stage III or Stage IV melanoma and evidence of disease progression. For the Cohort 1 the median estimate of PFS was 3.7 month and the 6-month PFS rate was 26.1%. The estimated Kaplan-Meier median OS was 8.9 months. The overall survival rate was 40.9% at 12 months and was not estimable at 18 and 24 months. The median follow-up time was 8.7 months. Based on assessments by the IRR, the disease control rate (DCR) was 52.7% and the CBR was 31.2%. The durable SD rate was 22.6%. The assessments for time to response and duration of response were not reliable given the small number of responses. For the Cohort 2 the median estimate of PFS was 1.8 months and the 6-month PFS rate was 17.2%. The estimated Kaplan-Meier median OS was 6.3 months. The overall survival rate was 26.8% at 12 months, 19.9% at 18 months and 16.4% at 24 months. The median follow-up time was 14.0 months. Based on assessments by the IRR, the DCR was 34.8% and the CBR was 14.6%. The durable SD rate was 5.6%. The assessments for time to response and duration of response were not reliable given the small number of responses.

In Study E7080-701, 7 subjects with platinum-sensitive ovarian cancer were enrolled. Due to the early termination of the study, no efficacy analysis was performed.

Although efficacy was not an endpoint for the Phase 1b portion of Study E7080-702, tumor response was recorded. The data presented were from local reads only; thus, caution should be used when interpreting the data. Some encouraging clinical activity was noted at the MTD (Cohort 2, 20 mg daily, n=7), with a best overall response of partial response (PR) for 2 subjects, stable disease (SD) for 4 subjects, and unevaluable for 1 subject.

Although Study E7080-702 was not powered or designed to determine superiority of the lenvatinib plus dacarbazine combination (L+D arm) compared with dacarbazine alone (D arm) in Phase 2, the study did provide promising efficacy results. The median PFS (imputed) for the L+D arm was 19.1 weeks (95% CI: 9.57, 25.57) compared with 7.0 weeks (95% CI: 5.57, 15.57) for the D arm, with a hazard ratio of L+D versus D alone of 0.4 (95% CI: 0.23, 0.75), a 2.7-fold increase in PFS, and 60% reduction in progression risk. Time to progression favored the L+D arm (n=30), with an imputed median TTP of 19.1 weeks (95% CI: 9.57, 24.43) compared with 7.0 weeks (95% CI: 5.57, 15.57) in the D arm (n=30), with a hazard ratio of L+D versus D alone of 0.4 (95% CI: 0.25, 0.79). In the L+D arm, 31 subjects (77.5%; 95% CI: 64.6%, 90.4%) were recorded as having PD or death at six months compared with 34 subjects (91.9%; 95% CI: 83.1%, 100.0%) in the D arm. An overall response (confirmed CR or PR) was reported for eight subjects (ORR: 20.0%; 95% CI: 7.6%, 32.4%) in the L+D arm compared with three subjects (ORR: 8.1%; 95% CI: 0.0%, 16.9%) in the D arm for an ORR difference comparing the L+D arm with the D arm of 11.9% (95% CI: -3.3%, 27.1%). In the L+D arm, the disease control rate (CR + PR + SD [confirmation of CR or PR not required]) was 60.0% (95% CI: 44.8%, 75.2%) compared with 40.5% (95% CI: 24.7%, 56.4%) in the D arm.

A meaningful clinical benefit was observed in Study E7080-G000-201. Lenvatinib showed antitumor activity in both the DTC and MTC histological cohorts. The primary endpoint of the study, ORR based on the assessments by the independent imaging review (IIR), was 50% in the DTC cohort and 36% in the MTC cohort. A favorable benefit was also observed in the secondary efficacy endpoints of median PFS and overall survival. For the DTC cohort, with a follow-up time of 14 months, the median estimate of PFS was 12.6 months, and for the MTC cohort, with a follow-up time of 8.0 months, the median estimate of PFS was 9.0 months. The overall survival rate was 86% for the DTC cohort and 76% for the MTC cohort at 12 months. These positive findings have led to pursuing a Phase 3 study, E7080-G000-303, in subjects with 131I-refractory DTC and radiographic evidence of disease progression within the prior 12 months.

The remaining 6 Phase 2 studies, (E7080-G000-205 in renal cell carcinoma (RCC), E7080-G000-207 in pediatrics subjects, E7080-G000-209 in adenocarcinoma, E7080-703 in locally advanced or metastatic NSCLC, and E7050-G000-901 in combination with lenvatinib in subjects with advanced solid tumors (Dose Escalation) and in subjects with recurrent glioblastoma or unresectable Stage III or Stage IV melanoma) are currently ongoing.

4.1.4.7.3 Phase III

Of the 2 Phase 3 studies, Study E7080-G000-303 is closed to enrollment and the data have been analyzed for the primary objective of efficacy. This is a Phase 3 study to compare the

safety and efficacy of lenvatinib in subjects with 131I-refractory DTC and radiographic evidence of disease progression within the prior 12 months. The study cutoff date for the primary analysis of this study was 15 Nov 2013. As of this date, 94 (36.0%) subjects in the lenvatinib arm and 119 (90.8%) subjects in the placebo arm had completed treatment in the Randomized Phase, i.e., had disease progression. Treatment was discontinued prematurely for 45 (17.2%) subjects in the lenvatinib arm and 4 (3.1%) subjects in the placebo arm. The most frequent reason for premature discontinuation in both treatment arms was AEs: 37 (14.2%) subjects in the lenvatinib arm and 3 (2.3%) subjects in the placebo arm. Treatment was ongoing for 122 (46.7%) lenvatinib subjects compared with 8 (6.1%) placebo subjects.

All 392 subjects enrolled in the study (261 in the lenvatinib arm and 131 in the placebo arm) were included in both the Full Analysis Set and the Safety Analysis Set. The Per Protocol Analysis Set comprised 383/392 (97.7%) subjects, 256/261 (98.1%) subjects in the lenvatinib arm and 127/131 (96.9%) subjects in the placebo arm.

Based on IIR assessments using the Full Analysis Set, the median PFS was 18.3 months for lenvatinib compared with 3.6 months for the placebo group, with an HR of 0.21 (99% CI: 0.14, 0.31), as estimated from the stratified Cox proportional hazard model. The difference in PFS between the lenvatinib and placebo arms was statistically significant (P<0.0001) using both a stratified and unstratified log-rank test.

The results of the primary efficacy analysis were fully supported by the results of the analysis with the Per Protocol Analysis Set. The median PFS and 95% CI were the same for the 2 analysis sets. The results of the 3 planned sensitivity analyses were consistent with the primary PFS analyses (Sensitivity Analysis A [all events and deaths], Sensitivity Analysis B [investigators' assessments], and Sensitivity Analysis C [uniform scheduled date of assessment]). The log-rank tests all showed a statistically significant difference between lenvatinib treatment and placebo (P<0.0001). The HRs for all the analyses were comparable (0.21 to 0.24).

The median PFS was longer with lenvatinib treatment compared with placebo for all of the subgroups evaluated (age group [≤65, >65 years], sex, race, prior VEGF/VEGFR-targeted therapy [0, 1], region [Europe, North America, Other], histology [papillary, follicular], and TSH level). The HRs and 2-sided 95% CIs showed favorable outcomes for lenvatinib compared with placebo for PFS for all the various subgroups.

Four (1.5%) subjects treated with lenvatinib had a best overall response (BOR) of CR while no subjects in the placebo group had a CR, and 165 (63.2%) subjects had a PR compared with 2 (1.5%) subjects in the placebo group. The secondary endpoint, ORR based on the IIR assessments, was significantly higher with lenvatinib treatment. The ORR was 64.8% in the lenvatinib arm compared with 1.5% in the placebo arm. The odds ratio was 28.87, which was statistically significant (P<0.0001) in favor of lenvatinib. The median duration of objective response for the lenvatinib arm was not yet reached at the time of data cutoff. Among the responders, 75% had a duration of response of greater than 9.4 months, and the median time to the first objective response was 2.0 months for the lenvatinib group.

Although OS was another secondary endpoint, the study was not designed to demonstrate a survival difference with the crossover design and limited statistical power. The analysis for OS included data from the placebo-treated subjects with confirmed disease progression who entered into the optional open label (OOL) Lenvatinib Treatment Period of the Extension Phase. At the data cutoff date, the median OS was not yet reached for either the lenvatinib arm or the placebo arm (including crossover subjects). When adjusted for the treatment crossover, using the pre-specified rank-preserving structural failure time (RPSFT) model, the HR was 0.62 (95% CI: 0.40, 1.00), showing a trend toward prolongation of OS with lenvatinib as compared with placebo. The difference in OS between the 2 treatment arms was marginally significant as determined using the resampling method (bootstrapping) (P=0.0510). The adjusted OS rates were numerically higher in the lenvatinib arm compared with the placebo crossover arm (6 months: 90.7% vs 85.3%, respectively; 12 months: 81.6% vs 70.0%, respectively; 18 months: 72.3% vs 63.0%, respectively). Using the unadjusted stratified Cox proportional hazard model, the HR was 0.73 (95% CI: 0.50, 1.07), showing a trend in favor of lenvatinib treatment for prolonged OS, as was observed with the adjusted model.

Study E7080-G000-304 in unresectable HCC is still ongoing as of the 27 Apr 2015 data cutoff date.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Background: Gastroesophageal Cancer

With an annual global incidence of more than 952,000 cases of gastric cancer (GC) and 456,000 cases of esophageal cancer (EC), upper GI malignancies are major worldwide cancer risks.[5] In the United States, predictions for 2015 call for 16,910 new cases of EC, with 15,690 deaths, and 26,370 new cases of GC, with 10,730 deaths.[6] Most patients diagnosed in the US unfortunately already have advanced incurable disease at the time of presentation. Standard cytotoxic chemotherapy with a fluoropyrimidine and platinum is typically used as first-line treatment for advanced gastroesophageal adenocarcinoma, with median survival ranging from 8 to 10 months. There is no standard second line treatment and quality of life and minimization of side effects are key considerations when choosing the therapeutic approach. Both single agent irinotecan and docetaxel have demonstrated a survival benefit compared with best supportive care, with median overall survival rates of 4-5 months.[7] There is a clear need for better treatment options in this refractory gastroesophageal cancer patient population.

4.2.1.2 Targeting Angiogenesis

Angiogenesis plays a major role in the development and progression of gastric cancer. It has been shown that expression of VEGFR2 is a prognostic factor correlated with poor prognosis.[8] Furthermore, the Gastric Cancer Genome Atlas Research Network (TCGA) has demonstrated how some subtypes of gastric cancer are associated with a recurrent amplification of the VEGF-A gene and with an elevated expression of the angiogenesis-related pathways.[9-11]

Clinically, angiogenesis inhibitors are active and beneficial in the treatment of advanced gastric cancer. A recent meta-analysis of 22 trials exploring targeted therapy for a total of 7,022 advanced gastric cancer patients demonstrated positive results for anti-angiogenic agents in terms of overall survival (HR 0.759; $P < 0.001$).[12] Ramucirumab, an anti-VEGFR2 monoclonal antibody, has been FDA approved as a single agent or in combination with paclitaxel for treatment of advanced gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. When used as a single agent median overall survival reached 5.2 months and in combination with paclitaxel 9.6 months.[13, 14] In addition, apatinib an oral VEGFR2 tyrosine kinase inhibitor was approved in China in December 2014 for use in advanced gastric patients who have failed two prior lines of chemotherapy, based on a survival benefit of nearly two months.[15] It is currently being investigated in multiple additional ongoing studies in China including earlier lines of therapy, in combination with chemotherapy and as a maintenance strategy.[16] Finally, regorafenib an oral multi-targeted tyrosine kinase inhibitor including VEGFR1-3, has demonstrated promising activity in refractory gastroesophageal patients. Led by the AGITG group, INTEGRATE was a randomized phase II study of regorafenib versus placebo in 152 advanced gastroesophageal cancer patients who had progressed on one or more lines of prior therapy. A significant improvement in progression free survival compared to placebo (2.6 vs 0.9 months, $p<0.0001$) was found in all geographic regions and patient subgroups evaluated.[17]

4.2.1.3 Immune Checkpoint Inhibition

There is increasing evidence that cancer immunotherapy is active in a wide variety of malignancies. Modulation of the immune checkpoint is one of the key mechanisms by which tumors are able to evade the immune response and escape destruction. Checkpoint pathways are regulated by ligand/receptor interactions. The programmed death-1 (PD-1) receptor is present on lymphocytes and negatively regulates T cell responses following binding of PD-1 ligand (PD-L1), which is frequently expressed on tumor cells. Blocking the PD-1/PD-L1 interaction prevents tumors from down regulating the cytotoxic lymphocyte response. Immune checkpoint inhibition has shown early promise in the treatment of gastric cancer. A phase 1b study of single agent pembrolizumab was reported in which patients with advanced PD-L1-positive gastric cancer who had progressed on at least 1 line of therapy were treated every 2 weeks until progression or toxicity. Pembrolizumab had manageable toxicity and demonstrated promising efficacy with a 22% response rate and a 12 month overall survival of 42%.[18] Single agent pembrolizumab was subsequently evaluated in a large phase II study of patients with advanced gastric/GEJ adenocarcinoma who had progressed on 2 or more prior chemotherapy regimens. Of 259 patients enrolled, overall response rate irrespective of tumor PD-L1 expression was 11.2%.[19] Grade 3-5 treatment-related adverse events were manageable and occurred in 16.6% of patients, leading to treatment discontinuation in 2 patients and fatalities in 2 patients. Nivolumab, a similar monoclonal antibody targeting PD-1, was investigated as a single agent in 59 refractory gastroesophageal cancer patients. Overall response rate was 12%, with a 12 month overall survival rate of 38%.[20] Single agent nivolumab was also evaluated in a randomized placebo controlled phase III study for patients with advanced gastric cancer who had progressed on 2 or more chemotherapy regimens. A total of 493 patients were enrolled and randomized 2:1 to nivolumab versus placebo with primary endpoint overall survival. Median OS was 5.32 months with nivolumab versus 4.14

months with placebo (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.50-0.78; p<0.0001), and OS rates at 6 and 12 month were 46.4% versus 34.7% and 26.6% versus 10.9%, respectively. The overall response rate (ORR) was 11.2% (95% CI, 7.7-15.6) with nivolumab versus 0% (95% CI, 0.0-2.8) with placebo (p<0.0001). Grade ≥ 3 drug-related adverse events (AEs) occurred in 11.5 % of nivolumab and 5.5 % of placebo; 2.7% and 2.5%, respectively, discontinued of study treatment due to drug-related AEs (any grade).[21]

4.2.1.4 Rationale for a Combined Anti-Angiogenesis and Immune Therapy Strategy

There is significant interplay between angiogenesis and the immune system. VEGF has been shown to exert multiple effects on the anti-tumor immune response including antigen presentation, effector mechanisms and immune cell trafficking. Specifically, VEGF can impair dendritic cell maturation through both VEGFR-1 and 2.[22-24] VEGF can also induce myeloid derived suppressor cell (MDSC) accumulation and regulatory T cell (Treg) proliferation in a VEGFR2 dependent manner.[25, 26] In addition, the extravasation of effector immune cells into tumor sites is modulated by VEGF. VEGF can down-regulate the expression of adhesion molecules, including ICAM 1 and VCAM-1, on tumor endothelial cells thereby limiting the leukocyte-endothelial interaction.[24] As a result, in the presence of a pro-angiogenic environment, the tumor microenvironment lacks adequate effector T cell infiltration and is characterized by hypoxia and acidity, conditions known to foster immunosuppressive cells. In turn, many of the induced immunosuppressive cells themselves promote angiogenesis. Both myeloid derived suppressor cells as well as activated dendritic cells directly support tumor neo-angiogenesis.[27-29]

Given the extensive cross talk between angiogenesis and immune surveillance, a combined and targeted approach is warranted for optimal outcomes. Employing anti-angiogenic therapy provides several advantages beyond its own potential anti-tumor effects. Because angiogenesis inhibitors do not deplete all Tregs, but only restore their proportion to physiologic levels, there is less likelihood of autoimmune mediated side effects.[26] In addition, targeting angiogenesis does not deplete activated T cells while it does inhibit immunosuppressive pathways such as MDSC's and thereby may promote the ideal environment for an immune modulated anti-tumor response.[30]

Proof of principle was demonstrated in a xenograft colon cancer model in which the simultaneous blockade of PD1 and VEGFR2 inhibited tumor growth synergistically, without any overt toxicities.[31] It was noted that VEGFR2 blockade did not interfere with T cell infiltration and immunological activation induced by PD-1 blockade. In this study, a monoclonal antibody to VEGFR2 was employed; however, it is hypothesized that a VEGFR2 TKI with additional targets would be superior. Sunitinib, a multi-targeted TKI with targets including VEGFR2, PDGFR and Flt3, demonstrated reversal of immune suppression and modulation of the tumor microenvironment in a colon xenograft model.[32] There was a decrease in the number of MDSC's and Tregs as well as an increase in CD8 and CD4 tumor infiltrating cells for sunitinib treated mice. There was also a decrease in expression of immunosuppressive cytokines such as IL-10 and TGF-β. Promising activity for combined PD-1 and VEGFR2 blockade has been seen in renal cell carcinoma. In a phase I clinical trial combining nivolumab, an anti-PD-1 antibody with sunitinib or pazopanib in patients with metastatic renal cell carcinoma the ORR was 52% (17/33) in the sunitinib arm and 45% (9/20)

in the pazopanib arm. Responses occurred by first assessment (6 weeks) in 41% (arm S) and 56% (arm P) of responding patients and were durable (range: arm S: 12.1+ to 54 weeks; arm P: 12.1 to 69.1+ weeks).[33]

4.2.1.5 Advantage of Lenvatinib in Gastroesophageal Cancer

Similar to other anti-angiogenic agents found to have single agent activity in advanced gastroesophageal cancer, lenvatinib inhibits VEGFR2 with a high affinity and an IC 50 of 4nM/L. However, lenvatinib also targets additional tyrosine kinases including FGFR. Fibroblast growth factor (FGF) family members are among those linked to escape from the effects of inhibition of VEGF signaling.[34, 35] Therefore, lenvatinib should theoretically provide superior anti-angiogenic activity than pure VEGF/VEFR2 inhibitors. In mice models, lenvatinib was shown to inhibit both VEGF- and FGF- induced angiogenesis.[2] Amongst an extended panel of 19 human tumor xenograft models, lenvatinib treatment resulted in significant tumor shrinkage with a ΔT/C of -55% in the AZ-521 gastric adenocarcinoma cell line. The anti-tumor activity of lenvatinib in these xenografts was associated with high microvessel density (MVD) and low % of pericyte coverage. Furthermore, when MVD and pericyte coverage were examined in 18 different types of human primary tumor specimens, stomach adenocarcinoma had one of the highest vascular scores and therefore would be predicted to be sensitive to treatment with lenvatinib.[2] Additionally, alterations in FGFR2 have been shown in up to 9% of gastric cancer patients and are correlated with poor outcome.[9, 36] Lenvatinib may be especially beneficial in this subset. Finally, it is interesting to note that both VEGFA and FGFR2 alterations are enriched in the chromosomal instability (CIN) and genomically stable (GS) molecular subsets defined by the TCGA.[9] More than two thirds of gastric cancers can be classified within these two subtypes which, unlike MSI and EBV subtypes, are not typically thought to be “immunogenic” tumors. Using lenvatinib to simultaneously target VEGF and FGF in these common subtypes is hypothesized to improve their “immunogenicity” and response to PD-1 blockade.

4.2.2 Rationale for Dose Selection

4.2.2.1 Pembrolizmuab Fixed Dosing

An open-label Phase I trial (Protocol 001) was 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.

4.2.2.2 Combined Pembrolizumab and Lenvatinib Dosing

An open label phase 1b/2 trial of lenvatinib plus pembrolizumab in subjects with selected solid tumors (NCT02501096) is currently ongoing. The phase 1b portion was designed to determine and confirm the maximum tolerated dose (MTD) for lenvatinib in combination with 200 mg (intravenous [IV], every 3 weeks [Q3W]) pembrolizumab in participants with selected solid tumors including non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, squamous cell carcinoma of the head and neck, or melanoma. Based on the preliminary results from this study, the MTD for lenvatinib was determined to be 20mg PO daily. In the first dosing cohort of lenvatinib 24mg po daily in combination with pembrolizumab 200mg IV q3w, 2 DLT's occurred including 1 grade 3 fatigue and 1 grade 3 arthralgia. As a result, the dose was de-escalated to 20mg of daily lenvatinib. At this dose level, no DLT's have been observed in 10 patients (6 with renal cell carcinoma, 2 with endometrial carcinoma, 1 with NSCLC and 1 with melanoma). Seven of the ten patients have not experienced any significant adverse events, have not required any dose reductions, and remain on study (range 4-19 weeks). Three patients did experience adverse events including one patient with grade 3 liver function abnormality at week 7 who came off study for progression of disease at week 9, one with grade 3 rhabdomyolysis at week 5 which resolved with holding treatment and patient currently continues on dose reduced treatment at week 9, and one patient with grade 3 hypertension at week 4. The study has now proceeded to the phase 2 expansion portion to evaluate the safety and efficacy of the combination in 6 cohorts with lenvatinib 20mg PO daily and pembrolizumab 200mg IV q3w.

4.2.3 Rationale for Study Endpoints

4.2.3.1 Efficacy Endpoints

Primary and Secondary Efficacy Assessments

Objective response as assessed by RECIST v1.1 are standard measures of clinical activity. Overall survival is considered the "gold standard" for quantifying clinical benefit, with PFS being an acceptable surrogate.

Safety

Standard safety parameters (AEs, SAEs, laboratory evaluations, vital signs, and physical examinations) will be employed to assess the safety profile of lenvatinib in combination with pembrolizumab.

4.2.3.2 Biomarker Research

Candidate biomarkers for subject selection will be assessed to determine whether these markers predict which subjects are most likely to respond to treatment with lenvatinib in combination with pembrolizumab.

Tumors can express PD-L1 as a mechanism of adaptive resistance to an activated immune response within the tumor microenvironment. PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in multiple tumor types including gastroesophageal cancer.[37] Archival pre-treatment biopsies will be collected from

all subjects and analyzed by IHC to evaluate whether the expression of PD-L1 may be a predictive marker for response to treatment with lenvatinib in combination with pembrolizumab.

Previous studies have demonstrated that certain gene expression profiles correlate with clinical benefit and represent reproducible and sensitive tools that define common features of the immune microenvironment associated with response to pembrolizumab across multiple tumor types.[18, 37] Commercially available nanostring technology will be used to look at a 770 gene panel which combines markers for 24 different immune cell types and populations, 30 common cancer antigens and genes that represent all categories of immune response including key checkpoint blockade genes. The 18 gene T-cell inflamed GEP (weighted sum of the normalized values for the genes) previously shown to be predictive of response to pembrolizumab will be determined.[37] The 6 gene IFN-γ signature will also be analyzed and correlated with clinical outcome. In addition, the genomic profile of the tissue will be analyzed to determine if there are alternations in various genes which may predict response, with special attention to the FGFR pathway.

The general status of the immune system may also affect responsiveness to combination treatment with lenvatinib and pembrolizumab. As a result, changes induced by lenvatinib in terms of immune cell phenotype, immune pathway activity, and profile of the immune response is planned to see if there is sensitization occurring to PD-1 inhibition. Blood will be collected for correlative biomarker analysis on study day 1 prior to initiation of lenvatinib. Repeat blood draws will be done on day 8, prior to pembrolizumab administration and on C2D1 prior to pembrolizumab administration. The numbers of total T cells, CD4T cells, CD8 T cells, B cells, and NK cells per mL of peripheral blood, the relative populations of these lymphocyte subsets, and the relative frequency of proliferating, naïve, effector, and memory T cells, will be evaluated by flow cytometry. Serum marker levels will be summarized descriptively and graphically for the patient population. The time course of expression levels will also be summarized graphically by patient.

4.2.4 Research Risks and Benefits

4.2.4.1 Other Risks of Study Participation

Additional risks to study participation include breach of confidentiality and risks associated with blood draw. This risk includes weakness, redness, pain, bruising, bleeding or infection at the needle site. Privacy protection procedures are in place and good clinical practice guidelines are followed for the study to minimize risks associated with research procedures and participation.

4.2.4.2 Potential benefits

The potential benefits to subjects with study participation are improved overall survival. The information obtained from this research may help others with this disease in the future.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis and Conditions for Entry into the Trial

Patients with advanced gastric and gastroesophageal junction(GEJ) adenocarcinomas who have progressed on one or more line(s) of therapy, but not more than 3 lines.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have histologically or cytologically confirmed metastatic or recurrent gastric or GEJ adenocarcinoma.
4. Have measurable disease based on RECIST 1.1.
5. Must have received and have progressed, or are intolerant to at least one systemic regimen (platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease or progressed within 6 month of completion of adjuvant therapy with a platinum- or fluoropyrimidine-based regimen).
6. If Her2 positive, must have received and have progressed or are intolerant to treatment with trastuzumab for metastatic or recurrent disease.
7. Subjects must consent to provide archival tumor tissue (initial and subsequent tumor biopsy samples, if possible) for correlative biomarker studies.
8. Have a performance status of 0 or 1 on the ECOG Performance Scale.
9. Adequately controlled blood pressure with or without antihypertensive medications defined as BP < 140/90 mmHg at screening and no change in antihypertensive mediation within 1 week prior to the Screening Visit.
10. Demonstrate adequate organ function as defined in Table 5, all screening labs should be performed within 10 days of treatment initiation.

Table 5: Adequate Organ Function Laboratory Values

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** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 3 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. Female subjects of childbearing potential (Section 5.5.2) must be willing to use an adequate method of contraception as outlined in Section 5.5.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

13. Male subjects of childbearing potential (Section 5.5.2) must agree to use an adequate method of contraception as outlined in Section 5.5.2 - Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is 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 treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (in dosing exceeding 10mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or lenvatinib or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, a minimum of four weeks must have passed and they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

8. Subjects having >1+ proteinuria on urine dipstick testing will undergo 24h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1g/24h will be ineligible.

9. Gastrointestinal malabsorption or any other condition in the opinion of the investigator that might affect the absorption of lenvatinib.

10. Prolongation of QTcF interval to >480ms

11. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug.

12. Arrhythmias requiring Class Ia and III antiarrhythmics and/or grade ≥2 bradycardia.

13. Bleeding disorders or active significant bleeding (i.e. hemoptysis, hematochezia, hematemesis) within 3 weeks.

14. Thrombotic disorders or use of anticoagulants, such as warfarin, requiring therapeutic international normalized ratio (INR) monitoring. (treatment with low molecular weight heparin (LMWH) or direct acting oral anti-coagulants is allowed.)

15. History of prior gastrointestinal fistula and/or perforation.

16. Has 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 trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

17. Has 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 and is allowed.

18. Has known history of, or any evidence of active, non-infectious pneumonitis.

19. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris.

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

21. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

22. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

23. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

24. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

26. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.1.4 Inclusion of Women and Minorities

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

5.2 Registration Procedures

5.2.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrolment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office. The following materials must be submitted to the Research Coordinator for registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be distinguished to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

5.2.2 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide a remote extensive monitoring including real-time review of all eCRFs to ensure

completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be completed within four weeks of enrollment. Decisions from the DSMB will be disseminated to other study sites during routine calls of the investigators at each site, which will occur monthly.

5.2.3 Patient Registrations at Other Participating Institutions

Enrollment at addition sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office and an SIV is conducted, an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyulangone.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyulangone.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within the designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Oberstein. Subjects must not start any protocol procedures prior to

registration; each participating institution will order the study agent directly from the supplier.

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy.

Please email all SAEs to NYUPCCsafetyreports@nyulangone.org, assigned medical monitor, and Dr. Paul Oberstein.

5.2.4 Process of Consent

Consent will be obtained by a participating investigator, or allied health professional/research coordinator/research nurse, all of whom have completed requisite training for human subject research and have been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients who are evaluated and/or treated by physicians in the oncology program will be given a consent form (attached) describing participation in the study. Patients will be given adequate time to read the consent form. After patients have been evaluated by their physician, they will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, physician's assistant, nurse, or research coordinator, all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYULMC PCC CTO guidelines and policy.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

5.2.5 Documentation of Consent

The Principal Investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

5.3 Trial Treatments

The treatment to be used in this trial is outlined below in Table 6

Table 6: Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Lenvatinib	20mg	QD	PO	Lead in as single agent day 1-7, then to continue daily on Q3 week schedule	Experimental
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle, starting following 7 day lead in with lenvatiinb (Day 8 of study)	Experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.3.1 Dose Selection and Modification

5.3.1.1 Dose Selection

Dose and schedule are based on phase I results from ongoing study "Phase 1b/2 Trial of Lenvatinib Plus Pembrolizumab in Subjects With Selected Solid Tumors" NCT02501096. Subjects with non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, squamous cell carcinoma of the head and neck, or melanoma were treated with pembrolizumab 200mg IV every three weeks with escalating doses of lenvatinib in order to determine the maximum tolerated dose. The MTD was determined to be 20mg of lenvatinib daily in combination with pembrolizumab.

5.3.1.2 Dose Modification (Escalation/Titration/Other)

If one therapeutic agent is either held or permanently discontinued secondary to toxicity, then therapy with the other study agent should continue and the subject should remain on-study with full adherence to all protocol-related requirements.

5.3.1.3 Dose Interruptions and Modifications for Pembrolizumab

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 drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 5.5.1 for supportive care guidelines, including use of corticosteroids.

Table 7: Dose Modification Guidelines for Pembrolizumab Adverse Events (AEs)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks Or 2nd episode
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

5.3.1.4 Dose Interruptions and Modifications for Lenvatinib

5.3.1.4.1 Management of Hypertension

Hypertension is a recognized side-effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP < 140/90 mmHg at the time of study entry and, if known to be hypertensive, are on antihypertensive therapy before they start treatment with lenvatinib. The early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as the BP is confirmed to be > 140/90 mmHg on 2 assessments 1 hour apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when BP > 140/90 mmHg is first observed on 2 assessments 1 hour apart. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.

Lenvatinib should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (e.g., BP > 160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the blood pressure is controlled, lenvatinib should be resumed as described below.

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

- Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.
- If systolic BP > 160 mmHg or diastolic BP > 100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a dose of 14 mg once daily when BP < 150/95 mmHg.
- If systolic BP > 160 mmHg or diastolic BP > 100 mmHg recurs on the 14 mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a dose of 10 mg once daily when BP < 150/95 mmHg.
- If systolic BP >160 mmHg or diastolic BP > 100 mmHg recurs on the 10mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and additional dose reduction should be discussed with the sponsor.

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

- Institute appropriate medical management.
- Discontinue lenvatinib

5.3.1.4.2 Management of Proteinuria

Regular assessment for proteinuria should be conducted as detailed in the Study Flow Chart (Section 6.0). Guidelines for assessment and management of proteinuria are summarized as follows:

- If proteinuria $\geq$ 2+ is detected on urine dipstick testing, study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be based on the 24 hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to the Dose Reduction and Interruption Instructions provided in Table 8.

Table 8: Dose Modification Guidelines for Lenvatinib-Related Adverse Events

Treatment-Related Toxicity[a,b]	During therapy	Adjusted Dose
Grade 1		
	Continue treatment	
Intolerable Grade 2[c]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once a day
Third occurrence(same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once a day
	Grade 3	
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once a day
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once a day
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	8 mg orally once a day
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with Sponsor
Grade 4[d]		
	Discontinue Study Treatment	

a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed.

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

c: Applicable to any grade 2 proteinuria and to Grade 2 toxicities judged by the subject and physician to be intolerable.

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

5.3.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.3.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor (NYU Langone Medical Center), investigator and subject will know the treatment administered.

5.4 Concomitant Medications and Vaccinations Allowed and Prohibited

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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.4.1 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 community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAEs) and events of clinical interest (ECIs) as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and lenvatinib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Replacement therapy (e.g., physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed with dosing not to exceed 10mg daily of prednisone equivalent.

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

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

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

5.5 Rescue Medications and Supportive Care

5.5.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.3.1.3 for dose modification.

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

Table 9: Dose Modification & Toxicity Management Guidelines for Immune Related AE's Associated with Pembrolizumab

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.

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 subjects for signs and symptoms of pneumonitis • Evaluate subjects 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		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with 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.
	Grade 4	Permanently discontinue		

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.

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
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 subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects 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 discontinue1		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue1		

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.

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
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. 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
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects 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 of T1DM).

5.5.2 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 10: 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 one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) 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. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6 Diet, Activity, and Other Considerations

5.6.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.6.2 Contraception

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

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

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

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

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

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

5.6.3 Use in Pregnancy

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

If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and Eisai followed as described above and in Section 5.6.3. The study investigator will make every effort to obtain permission from the male subject's female partner; to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

5.6.4 Use in Nursing Women

It is unknown whether pembrolizumab or lenvatinib are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial treatment for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 7.1.2.5

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.5.3.5.
- Unacceptable adverse experiences as described in Section 5.3
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 (Study Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8 Subject Replacement Strategy

There are no replacement subjects allowed.

5.9 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck and or Eisai decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TABLE 11: STUDY FLOW CHART

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment[m]**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 1)	Lead in D1-7	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Study Treatment (Tx.) Discontinuation (Discon.)	Safety Follow-up	Follow-Up Visits[n]	Survival Follow-Up[o]
Scheduling Window (Days):	-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Tx. Discon.	30 Days Post Tx. Discon.	Every 6-8 Weeks Post Tx. Discon.	Every 12 Weeks
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lenvatinib 20 mg PO QD[a]		X	X	X	X	X	X	X	X	X				
Pembrolizumab 200 mg IV Q 3 Weeks[b]			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status													X	X
Survival Status													X	X
Clinical Procedures/Assessments														
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review Pill Diary			X	X	X	X	X	X	X	X	X			
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram	X[p]													
Laboratory Procedures/Assessments														
Urine Pregnancy Test[q]	X													
Serum β-HCG Pregnancy Test[e‡]	X													
Coagulation Studies (PT/INR and aPTT) [‡]	X[+]													
CBC with Differential[f]	X[+]	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel[g]	X[+]	X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment[m]**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 1)	Lead in D1-7	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Study Treatment (Tx.) Discontinuation (Discon.)	Safety Follow-up	Follow-Up Visits[n]	Survival Follow-Up[o]
Scheduling Window (Days):	-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Tx. Discon.	30 Days Post Tx. Discon.	Every 6-8 Weeks Post Tx. Discon.	Every 12 Weeks
Urinalysis[h]	X[+]		X	X	X	X	X	X	X	X	X			
Thyroid Function Tests (T3, FT4 and TSH)[i]	X[+]		X		X		X		X		X	X	X	
Efficacy Measurements														
Tumor Imaging & Disease Assessment[j]	X				X			X					X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival or Newly Obtained Tissue Collection[k]	X													
Correlative Studies Blood Collection[l]		X	X	X										

[a]Lenvatinib 20 mg will be administered as a single agent by mouth each day on Days 1-7 as a lead in dose. Lenvatinib administration will continue daily on a Q3 week schedule in combination with pembrolizumab.

[b]Pembrolizumab 200 mg IV will be administered on Day 1 of Cycle 1 following the 7-day lead in with Lenvatinib, and on Day 1 of each subsequent 3-week cycle.

[C]Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only.

[d]ECOG performance status must be maintained at 0-1 on day of treatment initiation.

[e]A serum β-hCG pregnancy test is required for women of childbearing potential at screening only, within 14 days prior to first dose of treatment.

[+]Screening laboratory studies to be conducted within 14 days prior to start of protocol therapy.

[‡]Required at screening only.

[f]CBC with Differential includes: Hemoglobin, Hematocrit, Platelet Count, White Blood Cell Count (Total & Differential), Red Blood Cell Count, Absolute Neutrophil Count, and Absolute Lymphocyte Count.

[g]Complete Chemistry includes: Albumin, Alkaline Phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), CO_2/Bicarbonate, Calcium, Chloride, Glucose, Phosphorus, Potassium, Sodium, Total Bilirubin, Direct Bilirubin (if Total Bilirubin is elevated or greater than the upper limit of normal (ULN)), Total Protein, and Blood Urea Nitrogen

[h]Urinalysis includes: Blood, Glucose, Protein, Specific Gravity, and Microscopic Exam (if abnormal results are noted)

[i]Thyroid function test including thyroid stimulating hormone (TSH), triothhyronine (T3) (or free T3) and free thyroxine (FT4) to be done at screening, cycle 1day and then every other cycle, ie cycle 3, 5, 7 etc.

[j]Tumor imaging is to include CT of the chest, abdomen, and pelvis. The preferred method of assessment is CT with contrast. If this is contraindicated, CT without contrast is preferred over MRI. The same method of imaging is preferred for all subsequent tumor assessments. Scans and x-rays must be done <4 weeks prior to the start of therapy. Tumor assessments will be based on RECIST v1.1,

and will be performed approximately every 6-9 weeks. Timing of imaging will be based on the start of pembrolizumab on cycle 1, day 1. First imaging assessment will be done at 6 weeks, prior to cycle 3, day1. Next assessment will be done six weeks thereafter, prior to cycle 5, day1. Subsequent imaging will be done every 3 cycles (9 weeks) thereafter, ie prior to cycle 8, 11, 14 etc.

[k]Archived tumor specimens will be collected at study enrollment. Receipt of specimens is not required prior to initiating study treatment.

[l]Blood for correlative studies will be collected on Day 1 of lead in of lenvatinib and day 1 of Cycle 1 and on Day 1of Cycle 2. Blood will be collected before administration of study treatment.

[m]Subjects who attain a CR or complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment. Subjects who stop pembrolizumab with stable disease may continue treatment for up to 1 year if progression occurs after stopping study treatment, if the study remains open and the conditions in section 7.1.5.3.5 are met.

[n]Follow-Up: Subjects who discontinue study therapy for a reason other than disease progression will undergo radiologic assessment every 9 weeks (63 ± 7 Days) to monitor disease status. Throughout the Follow-Up period, information regarding disease status, subsequent antineoplastic therapy, and survival status will be collected.

[o]Survival Follow-Up will occur via telephone call every 12 weeks until death, withdrawal of consent, or end-of-study, whichever occurs first.

[p]At Screening only, unless as clinically indicated
[q]Within 72 hours prior to C1D1

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Study Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck and/or Eisai for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ approval opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.2 Clinical Procedures and Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a physical exam during the screening period and subsequent visits. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Study Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.5 Tumor Imaging and Assessment of Disease

Tumor assessments will be based on RECIST v1.1 and will be performed according to the schedule presented in Sections 6.0 and 7.0. Tumor assessments should include the following evaluations: physical examination and CT of chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

Measurability of Tumor Lesions
Tumor lesions will be categorized as follows:

• **Measurable 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:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)

• **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm in short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, and 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.

• **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

• **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Evaluation of Target Lesions

• **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).

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

• **Progressive Disease -** 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 may be considered progression.)

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

Evaluation of Non-target Lesions

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

• **Non-complete Response/Non-progressive Disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

• **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the 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. In the absence of measurable disease, change in nonmeasurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive study treatment until confirmed PD.

Evaluation of Overall Response

Treatment of subjects may continue
after the initial assessment of PD if the investigator determines the subject is clinically improving and is deriving benefit from treatment. In the absence of clinical deterioration, such modifications to the RECIST criteria may discourage the early discontinuation of pembrolizumab in combination with lenvatinib and provide a more complete evaluation of the combination activity than would be seen with conventional response criteria.

Table 11: Estimation of Overall Response: RECIST v. 1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
Complete response	Not evaluable	No	Partial response
Complete response	Non-complete response/ Non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable	No	Partial response
Stable disease	Non-progressive disease and not evaluable	No	Stable disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

Archived tumor specimens will be collected at study enrollment. Receipt of specimens is not required prior to initiating on study treatment.

A total of 15 unstained 5 micron slides cut from an FFPE tissue block will be collected. The sections will be treated as follows:

PDL-1 Immunohistochemistry (5 slides)

Tumor tissue for biomarker analysis should be provided as five (5) unstained slides cut from an FFPE tissue block. Three (3) sectioned slides per sample are necessary for H&E, PD-L1, and isotype control staining. The 4th and 5th sections are for a repeat staining if needed.

Please refer to MISP Sample handling manual for additional sampling handling and shipping instructions.

Biomarker samples will be stored for at least 10 years, linking keys of the subject's unique identification number to their PHI will be maintained by the principal investigator and stored on the NYULMC secure drive. A subject can withdraw their samples at any time, by making a formal request to the principal investigator in writing.

Multiplexed-gene expression profiling (5 slides)

Research biopsies will be subjected to RNA extraction and analysis to assess expression of immune-related genes. The NanoString technology is a variation on the DNA microarray, and permits analysis of up to 800 transcripts in a single reaction. This platform has been validated for application to both RNA from frozen tissue and RNA extracted from FFPE samples. The nCounter®PanCancer Immune Profile Panel developed by NanoString, Inc. allows analysis of 770 genes for 24 different immune cell types and populations, 30 common cancer antigens and functional markers including checkpoint blockade genes (http://www.nanostring.com/).

RNA will be isolated from 5 X 5um sections of formalin-fixed, paraffin embedded material. RNA will be extracted from tissue at the NYU Translational Research Laboratory using the RNeasy® kit (Qiagen). The resulting RNA will be quantified using a bioanalyzer and 250ng used for targeted gene expression analysis following manufacturer's protocols. The resulting data will be interrogated to establish whether a limited and defined gene-expression signature is predictive of clinical responses to therapy. The gene expression analysis will be performed at the NYU Genome Technology Center. We will plan to assess several immune signatures, including the immune signatures cited above, section 4.2.3.2.

Tumor Genomic analysis (5 slides)

Whole genome sequencing will be performed on tumor tissue. Nucleic acid will be obtained from tumor cellular material from 5x5um sections of formalin-fixed, paraffin embedded material using standard operating procedures and then analyzed at the NYU Genome

Technology Center, led by Adriana Heguy, PhD. Genomic alterations, with special attention to the FGFR and VEGFR pathways will be evaluated to determine if there are any associations with clinical outcome.

Peripheral Blood Collection

Blood will be collected for correlative biomarker analysis on study day 1 of the lead in phase, prior to initiation of lenvatinib. Repeat blood draws will be done on Cycle 1, day 1, prior to pembrolizumab administration and on C2D1 prior to pembrolizumab administration. Three tall 10ml K2 EDTA tubes will be collected at each aforementioned time point. Peripheral blood specimens for correlative studies will be submitted to Dr. Debra Morrison, Director of the NYU Office of Collaborative Science (OCS) Immune Monitoring Core for processing.

Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood to assess immune cell populations. Flow cytometry analysis will be done at the NYU Cytometry and Cell Sorting Laboratory. Surface staining with a panel of antibodies (CD3, CD4, CD8, CD25, FoxP3, CD11c, CD83, CD86, CD56) and intracytoplasmatic cytokine staining, followed by flow cytometry will be performed in order to identify different T cell populations, their activation status, and the production of different cytokines as well as other immune cell populations. Serum marker levels will be summarized descriptively and graphically for the subject population.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 12.

Table 12: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)† ‡
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR) ‡
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT‡
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total thriiodothyronine (T3)
Red Blood Cell Count	Carbon Dioxide	Microscopic exam *(If abnormal*	Free thyroxine (T4)
Absolute Neutrophil Count	*(CO_2 or bicarbonate)*	*results are noted)*	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Calcium		Blood for correlative studies
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. A serum pregnancy test will be required.

‡ Screening only

Laboratory tests for screening should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

A subject has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion. The investigator and sponsor have the right to discontinue a subject from the study treatment or withdraw a subject from the study at any time.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2: Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.3.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.2) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.3).

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Study Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

The study flow chart (Section 6.0) shows all procedures to be conducted at the screening visit. Screening procedures are required for subjects at initial enrollment.

The following will be performed during the screening period:

- Informed Consent
- Confirmation of Eligibility Criteria
- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Physical Examination
- Vital Signs (including Height)
- ECOG Performance Status

- Serum β-hCG Pregnancy Test for Women of Child-Bearing Potential
- PT/INR and aPTT
- Complete Blood Count (CBC) with Differential
- Comprehensive Serum Chemistry Panel
- Urinalysis
- Thyroid Function Tests (T3, FT4, and TSH)
- Tumor Imaging and Disease Assessment
- Archival or Newly Obtained Tissue Collection

7.1.5.2 Treatment Period

Procedures to be conducted during the treatment period are presented in study flow chart (Section 6.0) for Cycles 1-8 and beyond. All samples are collected pre-dose unless otherwise indicated.

The following will be performed during the treatment period:

7.1.5.2.1 Lead in with Lenvatinib, Day 1-7

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Physical Examination
- Vital Signs
- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel
- Blood Collection for Correlative Studies
- Administration of Lenvatinib 20 mg, by mouth, daily (given alone on Days 1-7)

7.1.5.2.2 Cycle 1 Day 1

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Review Pill Diary
- Physical Examination
- Vital Signs

- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel
- Thyroid Function Tests (T3, FT4, and TSH)
- Urinalysis
- Blood Collection for Correlative Studies (prior to treatment)
- Administration of Lenvatinib 20 mg, by mouth, daily, on a q 3 week schedule
- Administration of Pembrolizumab 200 mg IV

7.1.5.2.3 Cycle 2 Day 1

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Review Pill Diary
- Physical Examination
- Vital Signs
- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel
- Urinalysis
- Blood Collection for Correlative Studies (prior to treatment)
- Administration of Lenvatinib 20 mg, by mouth, daily, on a q 3 week schedule
- Administration of Pembrolizumab 200 mg IV, on Day 1 of each 3 week cycle

7.1.5.2.4 Day 1 of Each Subsequent Cycle

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Review Pill Diary
- Physical Examination
- Vital Signs
- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel

- Thyroid Function Tests (T3, FT4, and TSH) (odd cycles)
- Urinalysis
- Tumor Imaging and Disease Assessment (prior to Cycle 3, Cycle 5, and every 3 cycles [9weeks] thereafter, ie cycle 8, 11, 14, etc.)
- Administration of Lenvatinib 20 mg, by mouth, daily, on a q 3 week schedule
- Administration of Pembrolizumab 200 mg IV, on Day 1 of each 3 week cycle

7.1.5.3 Post-Treatment Visits

The study flow chart (Section 6.0) shows all procedures to be conducted during the end of treatment visit and follow-up period. All subjects are to complete the end of treatment visit, all follow-up visits, and be contacted for survival status in accordance with the schedule of study procedures. However, if a subject discontinues study treatment and moves onto alternative anticancer treatment, follow-up visits will no longer be required; however, survival follow-up assessments would be required as indicated in the schedule of study procedures unless the subject withdraws consent for further survival follow-up. Survival follow-up will continue until the end of study as defined as 5 years after the final subject is enrolled, or the date the study is closed by the sponsor, whichever occurs first.

7.1.5.3.1 End of Treatment Visit

The following will be performed at the **End-of-Treatment Visit**:

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Review of Pill Diary
- Physical Examination
- Vital Signs
- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel
- Thyroid Function Tests (T3, FT4, and TSH)

7.1.5.3.2 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever

comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.3.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

The following will be performed at the **Safety Follow-Up Visit** (30 days post study treatment discontinuation):

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Physical Examination
- Vital Signs
- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel
- Thyroid Function Tests (T3, FT4, and TSH)

7.1.5.3.3 Follow-up Visits

Study subjects will receive up to 24 months of Pembrolizumab, and then will continue on Lenvatinib only. Subjects will then be followed every 9 weeks (± 7 days) with radiologic imaging (CT scan or MRI). If a subject experiences disease progression on single agent lenvatinib, then that subject will have the option to restart Pembrolizumab if all the other criteria are met (please see section 7.1.5.3.5 below entitled "Second Course Phase (Retreatment Period)" for more information).

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.3.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.3.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.0 – Trial Flow Chart for Retreatment.

The following will be performed at **Follow-Up Visits** (every 6-8 weeks after study treatment discontinuation):

- Collection of Demographic Information and Medical History
- Collection of Prior and Concomitant Medication Information
- Collection of Adverse Event Information
- Physical Examination
- Vital Signs
- ECOG Performance Status
- CBC with Differential
- Comprehensive Serum Chemistry Panel
- Thyroid Function Tests (T3, FT4, and TSH)
- Tumor Imaging and Disease Assessment
- Collection of Post-Study Antineoplastic Therapy Information
- Collection of Survival Status Information

7.1.5.3.4 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The following will be performed during **Survival Follow-Up** telephone calls (every 12 weeks after confirmed disease progression or start of a new anti-cancer therapy until death, withdrawal of consent, or end of study, whichever occurs first):

- Collection of Post-Study Antineoplastic Therapy Information
- Collection of Survival Status Information

7.1.5.3.5 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy

- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any other anti-cancer treatment besides lenvatinib since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.5.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

An adverse event 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 study drug(s), is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. 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.

Adverse events may occur during the course of the use of investigational product(s) in clinical trials, or as 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 adverse event.

All adverse events 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.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Pembrolizumab Overdose: Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck.

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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Lenvatinib overdose: Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Eisai:

The highest tested doses of lenvatinib in clinical studies were 32 mg QD and 20 mg BID. There have been reports of overdose with lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. Adverse reactions associated with these reports were consistent with the AEs reported in clinical studies at the recommended 24 mg dose. There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib should be withheld and supportive care initiated. There is no specific antidote for overdose with lenvatinib. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in subjects receiving single doses of lenvatinib as high as 40 mg were similar to the adverse events reported in the clinical studies at the recommended dose for DTC and RCC.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Eisai, Inc.:

Eisai Medical Affairs
100 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 1-888-274-2378
Fax: -1-732-791-1111
Email: ESI_Safety@eisai.com

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.2.1 Reporting of 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 Sponsor's 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.

Should a pregnancy occur, it must be reported immediately to the regulatory specialist, research coordinator, and NYUPCCsafetyreport@nyumc.org in accordance with the procedures described below. Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication. This will be reported to the IRB if necessary.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of study drug(s) that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 13 for additional details regarding each of the above criteria.

All SAEs must be reported to the sponsor, NYU Langone Medical Center within 24 hours and to Merck Global Safety and Eisai within 2 working days.

Initial Report: within 24 hours:
The following events must be reported to the CTO via email within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Email: NYUPCCsafetyreports@nyumc.org
Tel: 212-263-4427

AND

Paul Oberstein, MD
The Laura and Isaac Perlmutter Cancer Center
NYU Langone Medical Center
160 East 34th Street
New York, NY, 10016
Telephone: (212) 731-6120
AND

PCC Assigned Medical Monitor

For the time period beginning when the consent form is signed until treatment allocation any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2. for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor (NYU Langone Medical Center) and within 2 working days to Merck Global Safety and Eisai if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.. for additional details) whether or not related to the investigational product(s), must be reported within 24 hours to the Sponsor (NYU Langone Medical Center) and within 2 working days to Merck Global Safety and Eisai.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to either investigational agent that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety and Eisai.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220 and

To Eisai, Inc.:

Eisai Medical Affairs
100 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 1-888-274-2378
Fax: -1-732-791-1111
Email: ESI_Safety@eisai.com

A copy of all Reports and Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

Additionally, an FDA MEDWATCH Form 3500A (download form and instructions at http://www.fda.gov/Safety/MEDWATCH/HowToReport/DownloadForms/ucm2007307.htm) must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site. If supplied as in a narrative format, the minimum information to be supplied is as follows:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

IND Safety Reports:

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:

  – associated with the use of the study drug
  – unexpected,
  – fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:

  – associated with the use of the study drug,
  – unexpected, and
  – serious, but not fatal or life-threatening

  -or-

  – a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

  – suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process

Adverse events may be submitted on FDA Form 3500A (download form and instructions at http://www.fda.gov/Safety/MEDWATCH/HowToReport/DownloadForms/ucm2007307.htm), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is as follows:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor (NYU Langone Medical Center) and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

This section also specifies the NYULMC IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or others, including adverse events. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – improving Human Subject Protection".

The NYU IRB address is:

NYU School of Medicine IRB

1 Park Avenue, 6th Floor

New York, NY 10016

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected:* *An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures:* *An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as noted above. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

7.2.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

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

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2. - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, 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.

7.2.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

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

7.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 13: Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.2.6 Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

The Principal Investigator is responsible for reporting all unexpected problems involving risk to participants or others to NYU Perlmutter Cancer Center CTO.

7.2.7 Stopping Rules

As no adverse events are anticipated given the low level of risk in this trial, there are no formalized stopping rules. However, should any serious and unexpected adverse events occur, the principal investigator will consider whether early stopping is appropriate.

7.2.8 Medical Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. The Data Safety and Monitoring Committee (DSMC) will review the study at least annually. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.2.8.1 Data and Safety Monitoring Plan

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by DSMC at least annually (from the date the first subject is enrolled), at dose escalation point and subsequent cohort activation, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc.

7.2.9 Monitoring of Other Participating Institutions

Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with a Site Investigator and staff. If remote EMR access is not available, then the Site Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high- priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular

communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan

The Simon optimal two-stage design to test the null hypothesis of <10% RR (CR+PR) versus the alternative hypothesis of >30% overall response rate requires an overall sample size of 29 subjects in order to achieve 80% power with a significance level of 5%. After testing the combination therapy on 10 response evaluable subjects in the first stage, the trial will be terminated if there are 1 or fewer responses. If there are 2 or more responses (including non-confirmed responses) the trial will continue on to second stage. A response evaluable subject is defined as having received both investigational agents for at least 2 cycles and had one CT scan for disease evaluation on therapy, or evidence of early (prior to 2 cycles) clear progression on physical examination, or death prior to 2 cycles. Best overall response for the interim analysis will be assessed up to 6 months on treatment. If the trial goes on to the second stage, then if there are 5 or fewer responses out of 29 response evaluable subjects, the combination therapy will be rejected. If there are 6 or more responses (including non-confirmed responses) over the entire treatment duration - the combination will be studied further.

At the end of the study, toxicities, as measured by the NCI CTCAE Version 4.03, will be described by frequency and grade, by cycle and over all cycles, with the maximum grade over all cycles used as the summary measure per patient. Overall response rates (defined as PR plus CR) will be estimated with exact 95% confidence intervals. PFS and OS will be described using Kaplan-Meier curves.

All subjects who receive at least one dose of the lenvatinib and/or pembrolizumab combination will be evaluable for toxicity.

Efficacy Measures

Response rate (RR): Best overall response will be calculated as the best response (CR or PR) recorded from the start of treatment for each subject, and will be used for the summaries of objective response. Best overall response will be determined programmatically based on the RECIST 1.1 criteria. For this study confirmation of response within 4 weeks will not be required.

Progression Free Survival (PFS): is defined as the interval between the date of start of treatment and the earlier date of objective disease progression per RECIST 1.1 criteria or death due to any cause in the absence of progression.

Overall Survival (OS): is calculated as the interval from the start of treatment to the date of subject death (any cause).

RECIST 1.1 assessments (including Target Lesion measurements) will be used to determine ORR and PFS. Imaging assessments will be made every 6-9 weeks.

Safety Measures

AEs and SAEs will be collected throughout the study from informed consent until 30 days after study treatment is discontinued. Investigators must continue to report all SAEs to the NYU CTO until 30 days after study treatment is discontinued.

If a subject discontinues study treatment for reasons other than disease progression, and therefore continues to have tumor assessments using RECIST following the 30 days after the last dose of the last study treatment, only study drug-, or study procedure-related SAEs will be captured until the subject is considered to have progressive disease.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs.

AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities).

Biomarker/Exploratory Objectives

All biomarker analyses will consist of descriptive statistical summaries at baseline (means, medians, standard deviations, quantiles, ranges, etc.) and graphical displays (e.g. boxplots). Similar summaries will be provided by changes from baseline and response status for each of the biomarkers under study. We will use non-parametric tests to assess the relationships between PDL1 status, gene expression profiles of interest, and response to combination treatment of pembrolizumab and lenvatinib. Outcome relationships will be largely explorative and descriptive.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Products

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies of pembrolizumab will be provided by Merck as summarized in Table 14.

Table 14: Pembrolizumab Product Description

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Clinical Supplies of lenvatinib will be provided by Eisai as summarized in Table 15.

Table 15: Lenvatinib Product Description

Product Name & Potency	Dosage Form
Lenvatinib 10 mg	Capsule
Lenvatinib 4mg	Capsule

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck and Eisai, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

All samples will be stored in a secure place. Samples will be identified by a unique identifier. The subject's name will not be used on the sample. This unique identifier will be put into the sponsor database and will link in the sponsor database only to de-identified subject data (subject number). Personal health information (PHI) will not be identifiable in the sponsor database or on the stored samples. Besides protecting confidentiality, this system will allow the sponsor to destroy the sample if the subject requests this. Samples will be retained and used until they are exhausted. The log to PHI will be maintained at the study site. Information will be stored in a secure, locked room and in a secure, password-protected database. Only approved study personnel will have access to the samples.

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Compliance with Financial Disclosure Requirements

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

10.3 Ethical Considerations, and Compliance with Law, Audit and Debarment

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH), US government regulations, international standards of Good Clinical Practice (GCP), applicable regulatory requirements, the sponsor policy on Bioethics and Human Biological Samples, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and will be provided sufficient information to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. The consenting process and documentation will follow Standard Operating Procedures of the NYU PCC CTO.

Treating investigators will obtain informed consent after explaining the study and answering all questions the subject or subject's legally authorized representative may have. Individuals who are authorized to obtain consent will be listed on the FDA form 1572, and may also be listed in the protocol and consent form document. If necessary, a translator and consent form in the subject's native language will be provided.

An IRB must approve the final study protocol, including the final version of the Informed Consent Form and any other written information to be provided to the subjects. The

investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB must be given in writing. The investigator must submit the written approval to the NYU CTO before enrollment of any subject into the study.

The IRB must approve all advertising used to recruit subjects for the study.

The NYU CTO must approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The NYU CTO will provide Principal Investigators with safety updates/reports according to local requirements.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

Weekly registration reports will be generated to monitor subject accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, and more frequently if indicated.

The site will be monitored as outlined in the study Monitoring Plan. The study Monitoring Plan outlines the description of monitoring approaches, frequency of monitoring, communication, documentation, and management of non-compliance.

All subjects who sign and informed consent document and are screened for entry into the study must be documented. Subjects who fail to meet eligibility criteria must have the reason(s) recorded in the subject's source documents.

10.6 Data Management

Data management support for this study will be provided by DataCore, a core resource at NYULMC that will provide comprehensive data management to facilitate efficient data collection, query management, data monitoring and cleaning, and database lock. DataCore will create electronic Case Report Forms (eCRF) using an electronic data capture (EDC) system, and will provide and maintain the Data Management Plan and Date Entry Guidelines for site staff in concert with the study biostatistic staff.

Clinical data during the subject visit will be entered directly into the EPIC Electronic Health Record system at NYU sites and at Bellevue sites, then transcribed by site staff (e.g., Clinical Research Associates) into the eCRF pages for the clinical study in the Data Management system. The DataCore Clinical Data Manager will monitor study data entry for completeness and validity, query site staff for data clarification of invalid or missing entries, and oversee data entry, data cleaning and database lock timelines. The DataCore SAS programmer will provide routine data quality reports to the study team including the Clinical Data Manager; standard and ad-hoc reports for the clinical study team; and provide the required datasets to Biostatistics for DSMC reports, interim and final analyses in an ongoing and ad-hoc basis.

10.6.1 Source Documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into the electronic data capture system. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess eligibility and disease status
2. Subject demographics
3. Concurrent medications
4. Treatment records
5. Adverse events

10.6.2 Data and Source Documentation

An electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned research coordinator, and CTO quality assurance specialists will have access to the database. The electronic database capture system is the primary data collection instrument for the study. All data requested in this system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

10.6.3 Case Report Forms

All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.6.4 Records Retention

The CTO's protocol for records retention will be followed. It is the investigator's responsibility to retain study essential documents for at least 3 years after the formal closure of the study.

10.7 Monitoring of the study, Auditing and Inspecting

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University Cancer Center. The DSMC operates based on the National Cancer Institute approved Charter. It is a multidisciplinary committee, consisting of clinical investigators/oncologists, biostatisticians, nurses and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials, that is responsible for monitoring safety, conduct, and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYU Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYU Perlmutter Cancer Center.

This phase II trial will be monitored by DSMC quarterly (from the date the first patient is enrolled), at times of pre-specified response assessment, and at the completion of the study, prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional interim reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review, Phase I/II committee review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

1. Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

2. DSMC, quarterly

3. IRB: An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

4. In addition, the quality assurance unit will monitor this trial extensively, including real-time review of all eCRFs to ensure completeness and compliance with the protocol,accuracy and consistency of the data, and adherence to ICH Guidelines for Good Clinical Practice (GCP). In addition, a first subject audit will be conducted within four weeks of enrollment.

Study Monitoring Plan

This study will be monitored according to the above monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all pertinent study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the sponsor, government regulatory bodies, and university compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices. The investigator will contact the PCC CTO immediately if contacted by a regulatory agency about an inspection at the center.

11.0 STUDY FINANCES

11.1 Funding Source

This protocol will be funded in part by Eisai. Drug will be provided by Eisai and Merck Pharmaceuticals.

11.2 Subject Stipends or Payments

There are no subject/patient payments or stipends for participation in this research study.

12.0 PUBLICATION PLAN

The study PI holds the primary responsibility for publication of the results of the study.

13.0 APPENDICES

13.1 Table 16: ECOG Performance Status

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.

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

13.2 Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

13.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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.

* As published in the European Journal of Cancer:

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.

In addition, volumetric analysis will be explored by central review for response assessment.

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