

**CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010**

DEPARTMENT OF MEDICAL ONCOLOGY

TITLE: A Phase 2 Trial of Neoadjuvant Chemoradiation with Pembrolizumab followed by pembrolizumab with lenvatinib in esophageal/gastroesophageal junction squamous cell and adenocarcinomas

CITY OF HOPE PROTOCOL NUMBER: IRB # 20742

PROTOCOL DATE: 11/30/22

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

COH Initial Approval	Protocol Dated 02/05/21	Packet: 00
Amendment 01	Protocol Dated 04/11/21	Packet: 01
Amendment 02	Protocol Dated 10/06/21 – Specimen processing	Packet: 02
Amendment 03	Protocol Dated 10/14/22 – PI Change -> Chen, MD	Packet: 03
Amendment 04	Protocol Dated 11/30/22 – PI Change -> Chung, MD	Packet: 04
Amendment 05 at Continuation	Protocol Dated 11/30/22	Packet: 05
Amendment 06	Protocol Dated 11/30/22 (TP Update)	Packet: 06
Amendment 07	Protocol Dated 11/30/22 (TP Update)	Packet: 07
Amendment 08 at Continuation	Protocol Dated 11/30/22 (TP Update)	Packet: 08

SITE:
STAGE (If applicable):
MODALITY:
TYPE:

PRINCIPAL INVESTIGATOR: Vincent Chung, M.D.

COLLABORATING INVESTIGATORS: Yi-Jen Chen, M.D.
Jae Kim, M.D.
Tim Synold, PharmD

PARTICIPATING CLINICIANS: Loretta Erhunmwunsee, M.D.
Marwan Fakih, M.D.
Gregory Idos, M.D.
Trilokesh Kidambi, M.D.
Daneng Li, M.D.
James Lin, M.D.
Dan Raz, M.D.
Dupinder Singh, M.D.
Yanghee Woo, M.D.

BIostatistician: Paul Frankel, Ph.D.



City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

A Phase 2 Trial of Neoadjuvant Chemoradiation with Pembrolizumab followed by pembrolizumab with lenvatinib in esophageal/gastroesophageal junction squamous cell and adenocarcinomas

Version Date: November 30, 2022
Protocol Version: 04
City of Hope #: 20742
Agents: Pembrolizumab, lenvatinib
IND Number: Pending
Sponsor/IND Holder: City of Hope
Funding Support: Internal Funds/Philanthropy
Industry Partner: Merck
Industry Partner Protocol ID: MISP59452
NCT Number: NCT04929392
Participating Sites: City of Hope (Duarte)

Principal Investigator

Vincent Chung, MD
Medical Oncology
City of Hope National Medical Center
T: 626-218-3494
Email: vchung@coh.org

Coordinating Center

Data Coordinating Center
City of Hope National Medical Center
T: (626)-256-4673 x 83968
Email: DCC@coh.org

PROTOCOL TEAM

COH Co-Investigators

Biostatistician/Co-Investigator

Paul Frankel, PhD
Dept. of Information Sciences
T: 626-258-5265
Email: pfrankel@coh.org

Co-Investigator

Timothy Synold, PharmD
Dept. of Cancer Biology
T: 626-256-2110
Email: tsynold@coh.org

Co-Investigator

T:
Email:

Co-Investigator

Ajay Goel, PhD, AGAF
Dept. of Molecular Diagnostics and
Experimental Therapeutics
T: (626)-218-5660
Email: ajgoel@coh.org

Co-Investigator

Yi-Jen Chen, MD., PhD
Dept. of Radiation Oncology
T: 626-218-2247
Email: yichen@coh.org

Co-Investigator

Jae Kim, MD
Dept. of Surgery
T: 626-218-7287
Email: jaekim@coh.org

Non-COH Co-Investigators

Co-Investigator

T:
Email:

Co-Investigator

T:
Email

COH-Participating Community Practice sites

Site Lead Investigator

T:
Email:

Site Lead Investigator

T:
Email:

EXPERIMENTAL DESIGN SCHEMA

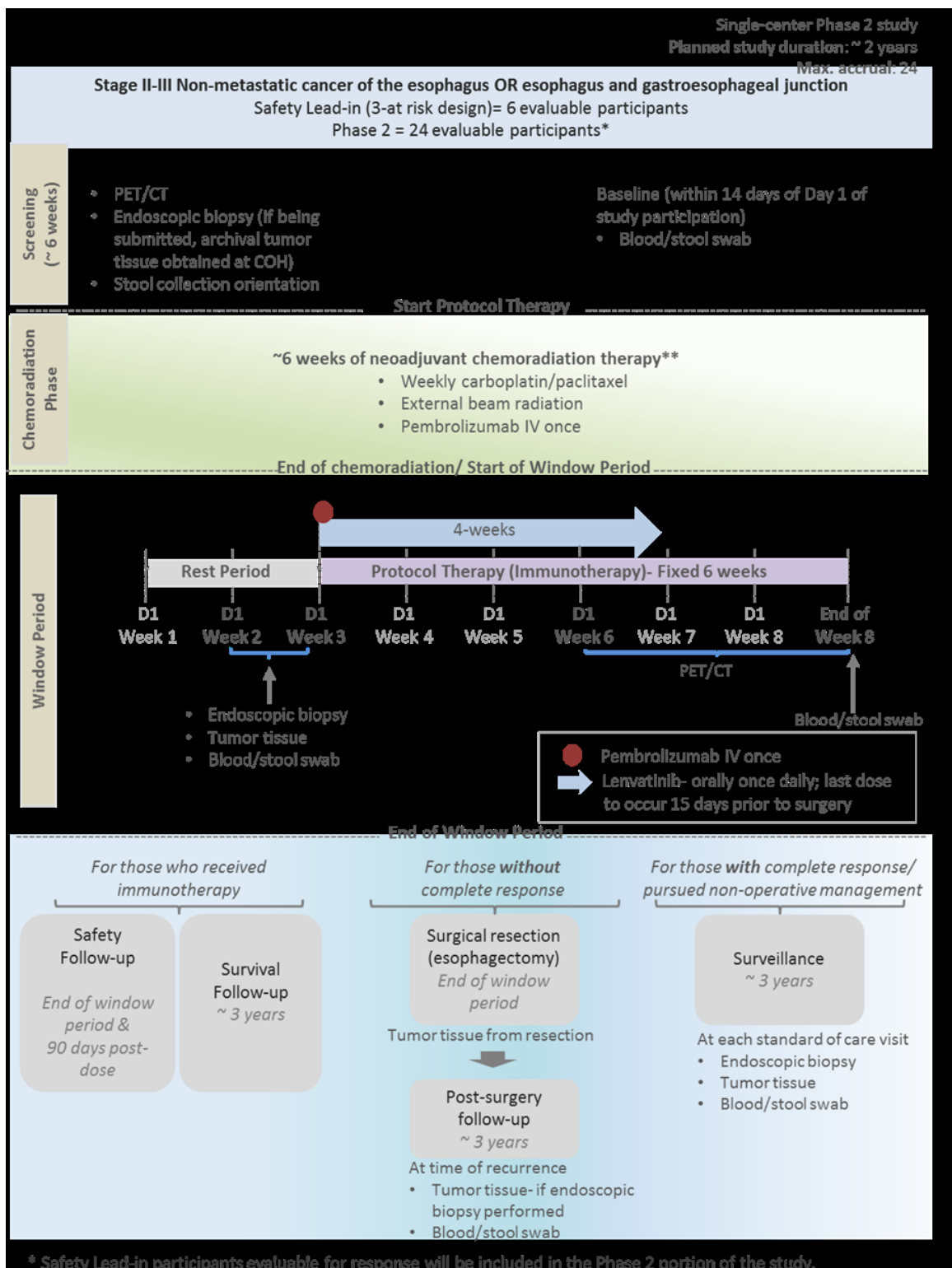


TABLE OF CONTENTS

SECTION	PAGE
Protocol Team	2
Experimental Design Schema	3
Table of Contents	4
List of Tables and Figures.....	5
Abbreviations.....	6
1.0 Objectives.....	7
2.0 Background.....	8
3.0 Eligibility Criteria	13
3.1 Inclusion Criteria	13
3.2 Exclusion Criteria	14
4.0 Participant Enrollment	16
5.0 Treatment Program	18
5.1 Treatment Program Overview	18
5.2 Safety Lead-In Cohort	18
5.3 Phase 2 Cohort.....	18
5.4 Chemoradiotherapy with Pembrolizumab Phase	18
5.5 Window Period: Protocol Treatment Plan.....	19
5.6 Protocol therapy Administration	20
5.7 Radiotherapy	21
5.8 Assessments and Special Monitoring	24
5.9 Duration of Protocol Therapy and Criteria for Removal from Protocol Therapy	24
5.10 Surgery/ Surveillance.....	25
5.11 Safety, Post-Surgery and Survival Follow-Up.....	25
5.12 Duration of Study Participation	26
5.13 Supportive Care, Prohibited and Concomitant Therapies/Medications.....	26
6.0 PROTOCOL THERAPY Dose Modification/ Delay Guidelines	28
6.1 Dose Modifications and Delays for Carboplatin/Paclitaxel during Chemoradiation	28
6.2 Criteria to Initiate Protocol Therapy During the Window Period	30
6.3 Dose Delay Guidelines for Pembrolizumab	31
6.4 Dose Delay/ Modification Guidelines for Lenvatinib	36
6.5 Dose Modifications for Overlapping Toxicities.....	40
7.0 Adverse Event List	42
8.0 Agent Information	44
9.0 Correlative/ Special Studies.....	51
9.1 Tumor Tissue Studies	51
9.2 Peripheral Blood Studies	53
9.3 Stool Samples	55
10.0 Study Calendar	57
11.0 Endpoint Definitions/Measurement of Effect	61
12.0 Statistical Considerations	63
12.1 Study Design	63
12.2 Evaluable Participants and Participant Replacement	64
12.3 Sample Size, Accrual Rate and Study Duration.....	64
12.4 Stopping Rules	64
12.5 Toxicity Monitoring after Safety Lead-in	65

12.6	Statistical Analysis Plan.....	65
13.0	Data Handling, Data Management, Record Keeping.....	66
13.1	Source Documents.....	66
13.2	Data Capture Methods and Management.....	66
13.3	Case Report Forms/Data Submission Schedule.....	66
13.4	Regulatory Records.....	66
14.0	Adverse Events and Unanticipated Problems Reporting	67
14.1	Assessment of Adverse Events	67
14.2	Reporting of Adverse Events	67
14.3	Adverse Events of Special Interest (AESIs).....	68
14.4	Overdose.....	68
14.5	Pregnancy and Breastfeeding	68
14.6	Abnormal liver function tests	69
14.7	Expedited Reporting	69
14.8	Reporting to Merck.....	69
15.0	Adherence to the Protocol & Reporting of Protocol Deviations	70
16.0	Study Oversight, Quality Assurance, & Data and Safety Monitoring	70
17.0	Ethical and Regulatory Considerations.....	72
18.0	References.....	77
	Appendix A: ECOG PERFORMANCE STATUS	79
	Appendix B: CONTRACEPTION GUIDELINES	80
	Appendix C-1: LENVATINIB PATIENT DRUG DIARY INSTRUCTIONS	81
	Appendix C-2: LENVATINIB PATIENT DRUG DIARY	82
	Appendix D: GUIDANCE FOR PATIENTS UNABLE TO SWALLOW WHOLE LENVATINIB TABLETS	86
	appendix e: FECAL SAMPLE COLLECTION INSTRUCTIONS (TO BE INCLUDED IN FECAL COLLECTION KIT)....	87

LIST OF TABLES AND FIGURES

Table 5.4: Chemoradiotherapy with Pembrolizumab Phase Intervention Plan.....	19
Table 5.5: Window Period Intervention Plan	20
Table 5.7.1 Regimen Description: Radiation.....	21
Table 5.9: Surgery/ Surveillance Plan.....	25
Table 6.1.1 Carboplatin and Paclitaxel Dose Levels	28
Table 6.1.2 Dose Modification for Hematologic Toxicities	28
Table 6.1.3 Dose Modification for Non-Hematologic Toxicities	28
Table 6.3.1 Dose Delay Guidelines for Pembrolizumab irAEs.....	31
Table 6.3.2 Dose Delay Guidelines and Management for Pembrolizumab Infusion Reactions.....	34
Table 6.4.1 Lenvatinib Dose Levels	36
Table 6.4.2 Dose Delay/Modification Guidelines for Lenvatinib AEs.....	36
Table 9.1 Tumor Tissue Studies Overview	51
Table 10.1 Study Activity Calendar – Screening and Chemoradiation Phase	57
Table 10.2 Study Activity Calendar – Window Period and Surgery/Surveillance Follow Up	59
Table 13.3 Data Submission Schedule	66
Table 14.6 Expedited Reporting Guidelines.....	69
Table 14.7. Timeframes for Reporting to Merck.....	69

ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Coordinator
CRF	Case Report Form
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
EOT	End of Treatment
FACS	Fluorescent Activated Cell Sorting
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
OIDRA	Office of IND Development and Regulatory Affairs
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Death 1 Receptor
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable disease

1.0 OBJECTIVES

1.1 Primary Objectives

- To evaluate pathologic complete response rate (path CR) and complete clinical response rate (clinical CR) at 14 weeks after starting chemoradiotherapy.

1.2 Secondary Objectives

- To assess safety and tolerability of pembrolizumab and lenvatinib in this patient population.
- To establish that pembrolizumab + lenvatinib will increase immune response via increased expression of the 18 gene pro-immune response signature measured using the Nanostring platform on tumor tissue biopsies.
- To evaluate disease-free (DFS) and overall survival (OS) in this study population.

1.3 Exploratory Objectives

- To identify through an integrated genomic sequencing approach (MHC-PepSeq) the presence of tumor mutations able to elicit neo-antigen-specific immunity in this population expected to be predominated by MSS tumors.
- To correlate temporal variations in ctDNA representing immunogenic and non-immunogenic mutations as pharmacodynamic immune markers.
- To correlate diversity in the gut microbiome with path CR and clinical CR in this study population.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Approximately 16,940 people are diagnosed with esophageal cancer each year in the United States and there are 15,690 deaths from the disease [1].

Neoadjuvant concurrent chemotherapy and radiation therapy has become an established standard of care in non-metastatic, locally advanced esophageal squamous cell and adenocarcinomas of the esophagus and gastroesophageal junction (GEJ) [2]. One commonly used chemotherapy regimen used concurrently with radiation includes weekly carboplatin and paclitaxel as established by the seminal Phase 3 CROSS trial, which observed a pathologic complete response rate of 23% in patients with adenocarcinomas and 49% in squamous cell carcinomas for an overall rate of 29% [3]. With the high pathologic complete responses seen with squamous cell carcinomas, older trials such as the French co-operative group FFCD 9102 trial appear to favor chemoradiation alone without surgery provided a clinical response to chemoradiation is achieved [4]. Longer term follow-up of patients enrolled on the FFCD 9102 trial in which clinical response to chemoradiation was not observed though underwent salvage surgery still demonstrated favorable survival outcomes [5]. As such chemoradiotherapy alone with close follow-up imaging and endoscopic biopsies for surveillance is also an accepted treatment approach in National Comprehensive Cancer Network (NCCN) guidelines [2]. The advantage with non-operative management and an organ-preservation approach is patients can avoid the morbidity and potential mortality associated with esophagectomy [6].

Post-neoadjuvant chemoradiation therapy, the current clinical practice at City of Hope in line with current national treatment guidelines is to give patients an 8-week window of no therapy (the window period) prior to proceeding to surgical resection to both permit recovery and potentially maximize tumor response. During this 8-week window patients undergo repeat PET/CT imaging as well as repeat endoscopic biopsy to ascertain patients who have achieved a complete response. Novel therapies that can be administered during this 8-week window period and lead to an increased incidence of patients who undergo non operative management due to complete response are needed.

This Phase 2 trial will explore the administration of neoadjuvant immunotherapy with pembrolizumab added to neoadjuvant chemoradiation and subsequent pembrolizumab combined with lenvatinib during the window period in the non-metastatic esophageal cancer setting.

2.2 Biological Rationale: Pembrolizumab and Lenvatinib

There is evidence to suggest that an immunosuppressive tumor microenvironment exists after chemoradiation [7] and the absence of any pathologic or clinical response to chemoradiation therapy may be accounted for by immunosuppressive mechanisms within the tumor microenvironment.

PD-L1 has been observed to be upregulated in preclinical models of radiation likely due to restraining of anti-tumor immune responses induced by radiation therapy [8-10]. Overexpression of both PD-L1 and PD-L2 has also been reported in both esophageal squamous cell and adenocarcinomas and is associated with poorer prognosis in squamous cell histology [11, 12]. Additionally neoadjuvant chemoradiotherapy was observed to increase PD-1 and PD-L1 tumor expression in 32% and 54%, respectively, of patients with GEJ tumors [7].

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.

Lenvatinib is a multiple receptor tyrosine kinase inhibitor with a potentially differentiated profile. It inhibits the 3 main vascular endothelial growth factor (VEGF) receptors (VEGFRs), VEGFR1, VEGFR2, and VEGFR3, as well as fibroblast growth factor (FGF) receptors (FGFRs), FGFR1, FGFR2, FGFR3, and FGFR4, platelet-derived growth factor receptor (PDGFR) α , c-kit, and the *RET* proto-oncogene, which play roles in tumor angiogenesis, tumor progression, and modification of tumor immunity. Once daily dosing of lenvatinib combined with pembrolizumab is currently being developed for the treatment of relapsed/refractory TNBC, ovarian cancer, gastric cancer, CRC, GBM and biliary tract cancers.

The effect of combining lenvatinib with anti-PD-1/PD-L1 mAbs has been investigated in the CT26 colorectal cancer syngeneic model as well as the LL/2 lung cancer syngeneic model. Combination treatment with lenvatinib and either an anti-PD-1 or anti-PD-L1 mAb showed significant and superior antitumor effects compared with either compound alone in these 2 syngeneic models.

This trial will take advantage of the window period to deliver lenvatinib and pembrolizumab to potentiate anti-tumor immune responses in an immunosuppressive microenvironment that may exist after chemoradiotherapy. Pembrolizumab together with lenvatinib is hypothesized to increase immune-mediated tumor cytotoxicity via an increase in tumor infiltrating and circulating cytotoxic T within the tumor microenvironment post- chemoradiotherapy. It is expected that the clinical outcomes for patients with esophageal cancer will be improved with neoadjuvant immunotherapy.

2.3 Pembrolizumab in combination with lenvatinib: Clinical Experience

Pembrolizumab in combination with lenvatinib has been granted accelerated approval by the Food and Drug Administration (FDA) in the United States for the treatment of patients with advanced endometrial carcinoma that is without high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR). This approval was based on Study 111/KEYNOTE-146 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting.[13] Patients were treated with lenvatinib 20 mg orally once daily in combination with pembrolizumab 200 mg administered intravenously every 3 weeks until unacceptable toxicity or disease progression. Among the 108 patients, 94 had tumors that were not MSI-H or dMMR, 11 had tumors that were MSI-H or dMMR, and in 3 patients the tumor MSI-H or dMMR status was not known. Tumor MSI status was determined using a polymerase chain reaction test. Tumor MMR status was determined using an immunohistochemistry test. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) by independent radiologic review committee using RECIST 1.1. The ORR in the 94 patients whose tumors were not MSI-H or dMMR was 38.3% (95% CI: 29%, 49%) with 10 complete responses (10.6%) and 26 partial responses (27.7%). Median DOR was not reached at the time of data cutoff and 25 patients (69% of responders) had response durations ≥ 6 months. In endometrial carcinoma, the most common adverse reactions (incidence $\geq 20\%$) for lenvatinib and pembrolizumab were fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. The most common $\geq$ grade 3 treatment-related adverse events were hypertension (32%), fatigue (8%), and diarrhea (7%).

2.4 Pembrolizumab 400 mg Q6week Dosing

Dosing of pembrolizumab at 400 mg every six weeks was granted accelerated approval by the FDA on April 28, 2020 for all currently approved adult indications, in addition to the current 200 mg every three weeks dosing regimen. The approval was based on pharmacokinetic modeling and exposure-response

analyses that compared the predicted exposure of pembrolizumab 400 mg every six weeks to observed exposures of pembrolizumab in patients who received pembrolizumab at 2 mg/kg every three weeks, 200 mg every three weeks, and 10 mg/kg administered every two weeks. The pharmacokinetic modeling were supported by additional exposure-response analyses across the pembrolizumab development program and an interim analysis of pharmacokinetics and overall response rate (ORR) in a cohort of patients (Cohort B) enrolled in Study KEYNOTE-555 (NCT03665597). Cohort B of Study KEYNOTE-555 was an international, single-arm, multi-center study that enrolled 101 patients with advanced or metastatic melanoma who had not received prior PD-1, PD-L1, or CTLA-4 inhibitors (other than CTLA-4 inhibitors in the adjuvant setting). The ORR was 39% (95% CI: 24, 55) in the first 44 patients enrolled in KEYNOTE-555. As such, further investigation of this alternative dosing schedule is attractive to increase adherence to pembrolizumab exposure in this trial where patients undergo 5-6 weeks of chemoradiation followed by an 8-week window period.

2.5 Overview and Rationale of Study Design

This is a single-center Phase 2 clinical trial with of neoadjuvant chemoradiotherapy with pembrolizumab followed by neoadjuvant pembrolizumab and lenvatinib for patients with non-metastatic esophageal squamous cell (SCC), adenocarcinomas (AC) of the esophagus and GEJ.

Precedence does exist in delivering PD-1 inhibitors with neoadjuvant chemoradiation for this indication. Kelly et al. presented at ASCO GI 2019 a neoadjuvant nivolumab study (2 doses q14 days prior to chemoradiation) followed by carboplatin/paclitaxel/radiation with 3 doses of concurrent nivolumab q14 days in 16 resectable esophageal/GEJ patients[14]. In addition to a promising pathologic CR rate, they did not observe that PD-1 inhibition led to delay or interference with surgery in any patients. However, as the combination of neoadjuvant pembrolizumab and lenvatinib prior to surgical resection is still novel, the trial will consist of a Safety Lead-in stage and a Phase 2 stage. During the Safety Lead-in, up to 6 evaluable participants will be enrolled using a 3-at risk design to evaluate safety/tolerability of pembrolizumab and lenvatinib in the neoadjuvant setting. Unacceptable toxicity will be evaluated during protocol therapy. If tolerable, participants will be enrolled to the Phase 2 stage to evaluate anti-tumor activity of this combination in the neoadjuvant setting.

Primary endpoint is pathologic complete response rate (path CR) and complete clinical response rate (clinical CR) at 14 weeks after starting chemoradiotherapy. Pathological response will be determined per College of American Pathologists Cancer Protocols and will utilize a modified Ryan scheme [15]. Post-therapy pathologic stage in esophageal cancer patients treated with neoadjuvant chemoradiation and surgery predicts for clinical outcome with pathologic complete responders demonstrating the most favorable survival [16]. We hypothesize synergistic anti-tumor activity with this combinatorial approach will relieve immunosuppression within the tumor microenvironment that may exist post-chemoradiotherapy.

A secondary efficacy endpoint will be measurement of immune response via interrogation of the 18 gene pro-immune response signature measured using the Nanostring platform on tumor tissue biopsies. Additionally, a co-secondary endpoint will be safety/ tolerability of neoadjuvant pembrolizumab and lenvatinib. Adult participants with two major histologies of esophageal cancer, squamous cell cancer (SCC) and adenocarcinoma will be enrolled to the trial, in addition participants with mixed adenosquamous carcinoma may enroll. Participants will have potentially resectable Stage I (T1N1 only) to Stage IVA cancer, deemed appropriate for neoadjuvant chemoradiation therapy and deemed appropriate for esophagectomy or repeat endoscopic biopsies if non-operative management is pursued.

Study Interventions

During the study, each participant will enter the following in the order described: (i) chemoradiotherapy phase (~6 weeks), (ii) window period (~8 weeks) which follows chemoradiotherapy and (iii) surgery/surveillance.

The chemoradiotherapy phase consists of (i) an endoscopic biopsy and (ii) neoadjuvant chemoradiotherapy (weekly carboplatin/paclitaxel plus 1 concurrent dose of pembrolizumab and external beam radiation). Since the primary endpoint is path CR and clinical CR at 14 weeks following chemotherapy, Day 1 of study participation will either be the endoscopic biopsy or initiation of chemoradiotherapy (if archival tissue fulfills tissue requirements).

The window period, consists of a (i) 2 week rest period during which time an endoscopic biopsy will be obtained, and (ii) fixed 4 weeks of protocol therapy with pembrolizumab-lenvatinib.

Participants will undergo standard of care management after the window period depending on their combined radiographic and pathological response status. Those without complete response will undergo esophagectomy. Those with complete response/ pursue non-operative management will undergo surveillance per frequency defined by the NCCN guidelines [2].

Protocol therapy

Participants will start protocol therapy with pembrolizumab in combination with chemoradiation. In line with the flat q6week dosing of pembrolizumab, patients will receive 400 mg IV pembrolizumab on Day 1 Week 1 of radiation. Protocol therapy will continue with lenvatinib and pembrolizumab commencing 14 days after completion of chemoradiation to ensure patients are sufficiently recovered from radiation-induced esophagitis. This corresponds to Week 3 of the window period and will help ensure patients can swallow lenvatinib tablets without difficulty.

Dosing and schedule for lenvatinib (20 mg orally once daily) with pembrolizumab is based on prior combination therapy with the regimen [13].

Participants will receive one dose of pembrolizumab on Day 1 Week 3 of the window period. The pembrolizumab dose in the window period will coincide with the first dose of lenvatinib therapy and provide immunomodulatory synergy to augment anti-tumor responses.

Participants will receive 28 days of lenvatinib therapy coinciding with beginning of Week 3 and end of Week 6 of the window period with the last dose of lenvatinib occurring minimum 15 days prior to surgery (i.e., no lenvatinib dosing for a minimum of 14 days prior to the surgery date). This will ensure in the context of this window-of-opportunity trial that patients achieve a therapeutic dose of protocol therapy but also have a sufficient time period to recover fully from any combination-induced toxicities with the known half-lives of these agents (pembrolizumab, $t_{1/2} \sim 3$ weeks; lenvatinib, $t_{1/2} \sim 28$ hours) and not compromise curative intent surgical resection.

All participants who receive protocol therapy will be followed for safety and survival.

Immune cell response

Endoscopic biopsies will utilize standard 3-6 mm biopsy forceps. As such tissue samples will be composed of both tumor cells and associated tumor stroma. Participants will have tumor samples in at least three timepoints: (i) baseline pre-treatment – this will provide the status of the cancer/tumor microenvironment prior to chemoradiotherapy, (ii) repeat endoscopic biopsy during Week 2 of window period – to assess the status of the immunosuppressive tumor microenvironment that occurs after pembrolizumab-based chemoradiotherapy and prior to start of combinatorial therapy, and (iii) at the time of surgical resection or during surveillance – to assess if successful abrogation of the immunosuppressive

tumor microenvironment has occurred with the utilization of pembrolizumab + lenvatinib therapy. For patients who achieve a complete clinical response the third timepoint will be replaced with serial follow-up endoscopic biopsies every 3 months for at least the first year unless there is development of local tumor recurrence. In such event patients will undergo salvage esophagectomy and a resected tumor sample will become available for biomarker analyses.

Using the Nanostring platform, the 18 gene pro-immune response signature will be utilized to determine if pembrolizumab + lenvatinib will increase immune-mediated tumor cytotoxicity via an increase in tumor infiltrating and circulating cytotoxic T cells within the tumor microenvironment post- chemoradiotherapy.

Exploratory correlatives

Comprehensive genomic tumor analysis: Exome, transcriptome sequencing, in silico neoantigen prediction of FFPE biopsies will be combined with the TGen MHC-PepSeq assay to identify tumor mutations that result in variant peptides capable of binding host HLA. The landscape of such mutations may be predictive of the response to the protocol therapy.

ctDNA samples: Non-invasive (ctDNA) assays measuring the abundance of different classes of the mutations characterized in comprehensive genomic tumor analysis will be developed for serial study of each individual and used to monitor the response over time. Disproportionate changes in the abundance of immunogenic v non-immunogenic mutations may provide a sensitive measure of immune pressure in response to the protocol therapy.

Serial stool samples: Characterization of the diversity of the gut microbiome is of interest since recent studies have correlated certain microbiome types with favorable responses to immune checkpoint blockade [17]. Microbial DNA will be extracted from stool swab samples and a 16S rRNA library for the MiSeq Illumina platform will be prepared. Microbiome sequencing data to analyze species diversity will be subsequently analyzed.

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

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

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

- __1. Documented informed consent of the participant and/or legally authorized representative.
- __2. Agreement to allow the use of archival tissue from diagnostic tumor biopsies
 - If unavailable, exceptions may be granted only with Study PI approval.

Age Criteria and Performance status

- __3. Age: ≥ 18 years
- __4. ECOG ≤ 1

Nature of Illness and Illness Related Criteria

- __5. Non-metastatic cancer of the esophagus OR esophagus and gastroesophageal junction (GEJ; tumor extending ≤ 2 cm into the stomach)
- __6. Confirmed Stage I (T1N1 only)-IVA diagnosis of **one** of the following:
 - Squamous cell; OR
 - Adenocarcinoma; OR
 - Mixed adenosquamous carcinoma.
- __7. Deemed appropriate for neoadjuvant chemoradiation by the multidisciplinary team (surgeon, medical oncologist, and radiation oncologist)
 - Chemotherapy defined as weekly carboplatin/paclitaxel; AND
 - Radiation defined as external beam radiotherapy defined as: 50.4 Gy as per institutional and national treatment guidelines
- __8. Deemed appropriate for esophagectomy or repeat endoscopic biopsies if non-operative management is pursued.

Clinical Laboratory and Organ Function Criteria (To be performed within 14 days prior to Day 1 of study participation/ 1st endoscopic biopsy unless otherwise stated)

__9. ANC $\geq 1500/\text{mm}^3$	ANC:	Date:
__10. Platelets $\geq 100,000/\text{mm}^3$	Plts:	Date:
__11. Serum total bilirubin $\leq 1.5 \times \text{ULN}$ OR Direct bilirubin $\leq \text{ULN}$ if total bilirubin levels $> 1.5 \times \text{ULN}$	ULN: Bil: Direct Bil:	Date:
__12. AST $\leq 2 \times \text{ULN}$	ULN: AST:	Date:
__13. ALT $\leq 2 \times \text{ULN}$	ULN: ALT:	Date:
__14. Creatinine $\leq 1.5 \times \text{ULN}$ OR for patients with Creatinine $> 1.5 \times \text{ULN}$ Creatinine clearance of ≥ 60	ULN: Serum Cr:	Date:

mL/min per 24 hour urine test or the Cockcroft-Gault formula $\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for females})$ Or $\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}} \quad (\times 0.85 \text{ for females})$	Cr Cl:	
__15. International normalized ratio (INR) or prothrombin time (PT) $\leq 1.5 \times \text{ULN}$	ULN: INR: PT:	Date:
__16. Activated partial thromboplastin time (aPTT) $\leq 1.5 \times \text{ULN}$	ULN: aPTT:	Date:
__17. <i>Female of childbearing potential only:</i> Negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine test: Serum test:	Date:

Contraception

__18. Agreement by WOCBP **and** males of childbearing potential* to use an effective method of birth control or abstain from heterosexual activity for the course of the study through at least 120 days after the last dose of protocol therapy.

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Exclusion CriteriaPrior and concomitant therapies

- __1. Immune checkpoint inhibitor(s) (e.g. anti-PD-1, anti-CTLA4).
- __2. Multi-tyrosine kinase inhibitor(s) (e.g. lenvatinib).
- __3. Radiotherapy within 21 days prior to Day 1 of study participation.
- __4. Investigational agent within 21 days prior to Day 1 of study participation.
- __5. Live-virus vaccination within 30 days prior to Day 1 of study participation.
- __6. Systemic cytotoxic chemotherapy, antineoplastic biologic therapy, or major surgery within 21 days of study participation.
- __7. Chronic systemic steroid therapy or on any other form of immunosuppressive medication.
- __8. Coumarin-based anticoagulants.

Other illnesses or conditions

- __9. Unstable or untreated brain/leptomeningeal metastasis.
- __10. Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal (GI) obstruction, or abdominal carcinomatosis (known risks factors for bowel perforation).
- __11. Severe hypersensitivity reaction to treatment with another antibody and/or hypersensitivity to lenvatinib and/or any of its excipients

__12. Active autoimmune disease that has required systemic treatment in the past 2 years.

__13. Known history of HIV, Hepatitis B or Hepatitis C (with confirmation of negative HBSAg, HBV PCR, and HCV PCR)

__14. History of pneumonitis (non-infectious) that required steroids or current pneumonitis

__15. Known history of active tuberculosis

__16. Diagnosed with or treated for cancer within the previous two years, other than histologies listed in inclusion criteria or non-melanoma carcinoma of the skin

__17. *Female only*: Pregnant or breastfeeding

__18. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__19. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	Print Name	Signature	Date
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other: _____			

*Eligibility should be confirmed per institutional policies.

4.0 PARTICIPANT ENROLLMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see [Section 17.4](#)), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in [Section 10.0](#).

4.2 Participant Enrollment

Eligible participants will be registered on the study centrally by the DCC at City of Hope. DCC staff are **available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays)**.

- Phone: (626) 256-4673 ext. 83968
- E-mail: DCC@coh.org

4.3 Slot verification and reservation

Designated study staff should call the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject. Slots can only be held for a limited time.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.4 Registration Process

To register a participant, the subsequent procedure is to be followed.

1. The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
 - Completed Eligibility Criteria List ([Section 3.0](#) of the protocol)
 - Source documentation to support eligibility criteria**
 - Signed informed consent document
 - Signed HIPAA authorization form (if separate from the informed consent document)
 - Signed subject's Bill of Rights

** Provide copies of source documentation only if not readily available as a finalized record in a COH Electronic Health Record (EHR).
3. After having received all transferred documentation, the DCC will complete their review of the documents to verify eligibility, working with the participating site as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.

4. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, registering the subject on study centrally into the COH clinical trials management system for non-COH participants, and enter the subject into the eCRF system.
5. Once registration has been completed, DCC staff will send a Confirmation of Registration Form within 24 hours, including the participant study number to:
 - The study team: treating investigator, protocol nurse, biostatistician, CRC and pharmacy
 - The COH sponsor team designees, including Study PI

4.5 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Issues that would cause treatment delays should be discussed with the Principal Investigator.

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate protocol therapy.

4.6 Dose Level Assignment

There are no dose level assignments.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a single-center Phase 2 clinical trial with neoadjuvant chemoradiotherapy with concurrent pembrolizumab followed by pembrolizumab and lenvatinib for patients with non-metastatic esophageal squamous cell (SCC) and adenocarcinomas (AC) of the esophagus and gastroesophageal junction (GEJ).

The study consists of 2 stages:

- **The Safety Lead-in stage** ([Section 5.2](#)) to evaluate safety/tolerability of pembrolizumab and lenvatinib in the neoadjuvant setting and
- **The Phase 2 stage** ([Section 5.3](#)) to evaluate anti-tumor activity when pembrolizumab and lenvatinib is added to the neoadjuvant setting

During the study, each participant will enter the following in the order described:

- **Chemoradiotherapy phase** ([Section 5.4](#)), which consists of neoadjuvant chemoradiotherapy with 1 concurrent dose of pembrolizumab;
- **Window period**, which consists of a (i) 2 week rest period during which time an endoscopic biopsy will be obtained, and (ii) protocol therapy with pembrolizumab-lenvatinib ([Section 5.5](#));
- **Surgery/ surveillance** ([Section 5.9](#)), where participants will be managed per standard of care.

Treatment will be administered in an outpatient basis. Follow-up for safety and survival will also occur ([Section 5.10](#))

Windows for all assessments and treatments are detailed in [Section 10.0](#).

5.2 Safety Lead-In Cohort

During the Safety Lead-in, up to 6 evaluable participants will be enrolled using a 3-at risk design.

Unacceptable toxicity will be evaluated during the period of neoadjuvant chemoradiotherapy through the window period up until the date of surgery or beginning of endoscopic surveillance for patients managed non-operatively ([Section 5.5](#) and [Section 11.1](#)).

5.3 Phase 2 Cohort

Once the Safety Lead-in is completed and protocol therapy is shown to be tolerable, additional patients will be enrolled. Patients enrolled during the Safety Lead-in will be included in the Phase 2 portion of the study if they are evaluable for response.

In the absence of study holds in accrual due to toxicity, 24 evaluable Phase 2 participants will be treated.

Phase 2 participants will continue to be monitored for unacceptable toxicity ([Section 5.5](#) and [Section 11.1](#)).

See [Section 12.0](#) for details.

5.4 Chemoradiotherapy with Pembrolizumab Phase

The endoscopic biopsy* will be obtained within 6 weeks prior to initiating neoadjuvant chemoradiotherapy with Pembrolizumab ([Table 5.4](#)). Day 1 of study participation is defined as the initiation of chemoradiotherapy.

*Archival biopsies obtained at COH can fulfill this timepoint (i.e. obtained before informed consent) with Day 1 of study participation still defined as the initiation of chemoradiotherapy.

Post-chemoradiotherapy, all participants will enter the window period.

Table 5.4: Chemoradiotherapy with Pembrolizumab Phase Intervention Plan

Intervention		Dose, Schedule & Route	Planned Intervention Duration
Chemoradiotherapy + immunotherapy	Carboplatin/paclitaxel	Weekly per standard of care and package insert	5 weeks
	Pembrolizumab	400 mg IV infusion over 30 minutes, 1 dose	Day 1 Week 1 of radiation
	External beam radiation	Total dose of 50.4 Gray per institutional and national treatment guidelines	~6 weeks

5.5 Window Period: Protocol Treatment Plan

The window period is approximately 8 weeks in duration and follows the chemoradiotherapy plus Pembrolizumab phase. The window period is further subdivided into **(i)** the rest period (first 2 weeks) and **(ii)** a fixed 6-week protocol therapy phase (See [Table 5.5](#)).

All participants will undergo a standard of care endoscopic biopsy during the second week of the rest period.

Day 1 Week 3 of the window period will be defined as the initiation of protocol therapy with pembrolizumab and lenvatinib (See [Table 5.5](#)). Participants **must meet criteria** to initiate protocol therapy ([Section 6.2](#)). See [Section 5.6](#) for agent administration details.

After the window period participants will enter the surgery/ surveillance phase ([Section 5.9](#)).

All participants who received protocol therapy will enter safety and survival follow-up ([Section 5.10](#)).

Table 5.5: Window Period Intervention Plan

Agent/Intervention		Dose	Route	Schedule	Planned Intervention Duration during Window Period
Endoscopic biopsy		N/A			Anytime during Week 2
Protocol window therapy	Pembrolizumab	400 mg	IV Infusion over 30 minutes	1 dose	Day 1 of Week 3
	Lenvatinib	20 mg	Orally	Once daily	Weeks 3-6 (last dose occurring 15 days prior to surgery)

5.6 Protocol therapy Administration

5.6.1 Pembrolizumab

When combined with lenvatinib, pembrolizumab will be administered **before** the lenvatinib dose.

The pembrolizumab dose is fixed at 400 mg.

See [Section 8.1.10](#) for preparation.

- The following infusion set materials are compatible with pembrolizumab:
 - PVC Infusion set that is plasticized using DEHP
 - PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
 - Polyethylene lined PVC infusion set
 - PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
 - Polyurethane set

*Contact Merck for materials not listed above
- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles.
 - If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line
 - Note:** the materials of the extension line and filter should be as mentioned above.
- Pembrolizumab (400 mg) will be administered as a 30 minute IV infusion per [Table 5.5](#).
 - Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).
 - Do not** administer the product as an IV push or bolus.
 - Do not** combine, dilute or administer it as an infusion with other medical products.

Management and dose delays associated with pembrolizumab AEs are outlined in [Section 6.2](#).

5.6.2 Lenvatinib

Lenvatinib will be administered **after** the pembrolizumab dose.

Lenvatinib should be taken:

- Orally, once daily, at the same time each day with or without food.
- Swallowed whole with water.

For special guidance for patients unable to swallow whole lenvatinib tablets, see [Appendix D](#).

If a participant misses a dose, then the participant is to take it as soon as he or she remembers. If the next scheduled dose is within 12 hours, the missed dose will be skipped and will not be made up. Doses that are vomited will not be made up.

Participants will be given a drug diary to document each dose of lenvatinib that is taken or missed ([Appendix C](#)).

Management and dose modification associated with lenvatinib adverse events are outlined in [Section 6.4](#).

5.7 Radiotherapy

Summary: Total dose of radiation will be 5040 cGy in 180 cGy fractions ([Table 5.7.1](#)).

Table 5.7.1 Regimen Description: Radiation

Radiation Therapy	Dose	Schedule
	5040 cGy in 28 fractions of 180 cGy	28 daily fractions administered Weeks 1–6

Technical Factors: Linear accelerators with a minimum energy of 6-15 MV will be used. A multiple field 3-D conformal technique or intensity modulated radiation therapy (IMRT) will be used. All fields will be treated each day. The patient will be treated in the supine position. Radiation will be delivered 5 days/week, once per day.

CT-based conformal planning is required on this study. In accordance with current guidelines for use of IMRT in clinical trials (see <http://qarc.org/>), IMRT may be used only if the degree of tumor motion is assessed and can be limited to 1.0 cm or techniques are used to compensate for respiratory motion.

Protocol Treatment Volumes: A volumetric treatment planning CT study will be required for this study. Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, with 3-5 mm thickness, will be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. A measurement scale for the CT image shall be included.

Gross Tumor Volume (GTV): The GTV is based on initial extent of disease using PET/CT scan, endoscopy report, and CT scan. The entire esophageal wall, including any disease that has extended through the wall should be contoured as the GTV as well as any PET/CT-avid or enlarged lymph nodes.

Clinical Target Volume (CTV): The intent of pre-operative treatment is to include the tumor plus the nodal groups at risk (whether clinically positive or negative). The CTV should encompass the peri-esophageal lymph nodes, mediastinal lymph nodes for mid- and upper- thoracic esophageal tumors, and the submucosal spread longitudinally along the esophagus. This is generally a 3-4 cm expansion on the GTV superiorly and inferiorly and 1.0 cm expansion radially. For distal esophageal tumors and GE junction tumors, the CTV should include the celiac lymph nodes. For tumors above the carina, the supraclavicular lymph nodes should be included in the CTV.

Planning Target Volume (PTV): The PTV is established by expanding the CTV by 0.5 cm in all directions. This will result in a margin of up to 5 cm superior and inferior and approximately 1.0-2 cm radially to the extent of tumor (GTV). For distal esophageal and GE junction tumors where motion management is not being used, the superior-inferior expansion can be 0.7-1.0 cm to account for the respiratory motion.

Target Dose Constraints:

Dose Prescription: The prescribed dose to the PTV is 5040 cGy delivered in 180 cGy/day over 28 fractions, to be administered during Weeks 4 to 8, ideally 5 fractions from Monday to Friday during Weeks 4-7 and Monday to Wednesday during Week 8.

Dose Uniformity: The dose to 99% of the PTV must be at least 93% of the prescribed dose, and a contiguous volume of no more than 2cc inside the PTV may exceed 20% of the prescribed dose.

Tissue Heterogeneity: Calculation shall take into account the effects of tissue heterogeneities. Planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo.

Normal tissue Dose Constraints: The normal structures to be contoured will depend on the level of the esophagus involved, but can include left and right lungs, heart, esophagus, brachial plexus, left and right kidneys, liver, stomach, small intestine, and spinal canal. The dose to normal tissues must be kept within the parameters described below.

1. Lungs

- a. V20Gy $\leq$ 20%
- b. and V30Gy $\leq$ 15%
- c. and V40Gy $\leq$ 10%
- d. V10Gy $\leq$ 40%
- e. V5Gy <60%

2. Cord

- a. Max $\leq$ 4500 cGy

3. Bowel

- a. Max bowel dose < Max PTV dose
- b. and D05 $\leq$ 45 Gy

4. Heart

- a. V40Gy $\leq$ 50%
- b. Mean <3000 cGy

5. L and R kidney:

- a. No more than 33% of the volume can receive 1800 cGy

6. Liver

- a. V20Gy $\leq$ 30 %
- b. V30Gy $\leq$ 20 %

c. mean <21 Gy

7. Stomach

a. Mean <3000 cGy (if not within PTV)

b. Max dose <54 Gy

Treatment Planning:

Simulation: Patients will be positioned supine with arms above the head. A CT simulation will be performed using 3-5 mm slice thickness. In patients for whom treatment will be delivered using respiratory gating or tracking, 4-dimensional CT scan should be used, and it is recommended the planning CT scan be performed with the patient in a breath-hold in end expiration.

Motion Management: For distal esophageal and GE junction tumors, respiratory motion can be significant, requiring an assessment of the degree of tumor motion at the time of simulation. To determine the extent of respiratory motion, a respiratory correlated CT scan may be obtained at the time of simulation. This scan will be performed throughout the breathing cycle (i.e., 4-dimensional CT) so that separate CT data sets associated with each phase of respiration can later be reconstructed. Treatment delivery can be done using the motion management technique available at the institution and can include treatment during free-breathing as long as an internal target volume has been designed based on the motion of the tumor on the 4D-CT.

Beam Arrangements:

1. 3D Conformal Beam Arrangements: Beam arrangement selection for 3D conformal treatment will vary based on the shape, size, and location of the CTV and the resulting PTV in relation to normal organs.

2. IMRT - Beam Arrangement: A five-field beam arrangement or volumetric modulated arc therapy including helical tomotherapy is preferred and it is essential to minimize the low dose distributed to the lungs. Suggested beam arrangements are:

a. For distal esophagus the following beam arrangement is useful for minimizing dose to the heart and lungs: left posterior-anterior oblique (155), left anterior-posterior oblique (LAO; 70-80), anteroposterior (0), right anterior-posterior oblique (RAO; 280-290), right posterior-anterior oblique (205)

Note that the range of gantry angles for the LAO and RAO fields is due to the fact that one needs to find the best compromise between the amount of heart and lung in the field.

b. For GE-junction esophagus, the following beam arrangement may be substituted if it is better for minimizing dose to the kidney. All beams are 15 MVx: posteroanterior (180°), close to left lateral (90°±10°), LAO (30-35°), RAO (325-330°), close to right lateral (270°±10°). All beams are 15 MV X-ray beams.

These recommended beam arrangements may be changed to one more fitting for the patient's particular anatomy.

Field verification: As a minimum requirement, verification images are obtained at the start of treatment and at least each week thereafter. Patients treated with IMRT should have daily imaging verification. Prior to the first treatment, images that verify the position of the isocenter placement must be obtained. Imaging can consist of portal or orthogonal images, or cone beam CT.

Definitions of Deviations in Protocol Performance

Prescription Dose

- No Deviation: $\geq 99\%$ of the PTV receives $\geq 93\%$ of the prescribed dose, and a contiguous volume of no more than 2cc inside PTV exceeds 20% of the prescribed dose.
- Minor Deviation: Deviations of this magnitude are not desirable, but are acceptable. Coverage that is equal to 93% of the prescribed dose and falls between 99% and 95% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 20-25% of the prescribed dose.
- Major Deviation: Doses in this region are not acceptable. More than 1 cm³ of tissue outside the PTV receives $\geq 120\%$ of the prescribed dose, or 93% of the prescribed dose falls below 95% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 25% of the prescribed dose.

Volume

- Minor Deviation: Margins less than specified, or field(s) 1-3 cm greater than specified.
- Major Deviation: Fields transect tumor or specified target volume(s), or fields are more than 3 cm greater than specified.

Critical Organ

- Major Deviation: The maximum dose to the spinal cord exceeds 4500 cGy; the heart mean dose exceeds 3000 cGy; the lung V20 exceeds 30% or the V10 exceeds 50%
- Minor Deviation: The lung V20 exceeds 20% or the V10 exceeds 40%

Treatment Interruption

- Minor Deviation: Treatment interruptions between five and nine normally scheduled treatment days.
- Major Deviations: Treatment interruptions totaling more than nine normal scheduled treatment days.

5.8 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see [Section 10.0](#).

It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator.

5.8.1 Special Monitoring

Adverse events 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 pembrolizumab. Refer to Section 6.3 for further details of immune-mediated toxicities.

5.9 Duration of Protocol Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy, defined as pembrolizumab and lenvatinib until one of the below criteria are met:

- Completed protocol therapy - 1 dose of pembrolizumab with chemoradiation followed by 1 dose of pembrolizumab and daily lenvatinib up to 15 days from surgery

- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy ([Section 17.5](#))

Once participants meet criteria for removal from protocol therapy and undergo all window period assessments, the participant should then proceed to Safety/ Survival follow-up ([Section 5.9](#)).

NOTE: All participants must continue to **undergo all window period assessments** as specified in the Study Calendar ([Section 10.0](#)) regardless of whether they received all of the planned immunotherapy.

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF. The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.10 Surgery/ Surveillance

Participants will undergo standard of care management after the window period depending on their combined radiographic and pathological response status ([Table 5.9](#)).

Table 5.9: Surgery/ Surveillance Plan

Response Status	Intervention	Planned Intervention Duration
For those without complete response	Surgical resection (esophagectomy)	N/A
For those with complete response/ pursue non-operative management	Surveillance- follow-up via periodic endoscopic biopsy	The 1st surveillance biopsy to occur within 1 month of ending the window period, then every 3 months from the 1 st surveillance biopsy for the 1 st year; every 4 months for the 2 nd year; every 6 months for the 3 rd year.

5.11 Safety, Post-Surgery and Survival Follow-Up

Safety, post-surgery and survival follow-up may occur in parallel with surgery/ surveillance:

- **Safety Follow-up-** for all participants who received protocol therapy to occur **(i)** end of Week 8 of window period **AND (ii)** 90 days post-last dose of protocol therapy OR until initiation of a new anticancer therapy (whichever occurs sooner)
 - **Note** the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Post-Surgery Follow-up-** for all study participants who underwent surgical resection.
- **Survival Follow-up-** for all study participants who received protocol therapy

Assessment time points and windows are detailed in [Section 10.0](#).

5.12 Duration of Study Participation

Participants **will complete** study participation when then they complete **(i)** planned neoadjuvant therapy (chemotherapy and protocol therapy) AND **(ii)** ~3 years of survival follow-up, surveillance or post-surgery follow-up, whichever comes first.

Criteria for discontinuing study participation before then include:

- Withdrawal of consent for continued participation (See [Section 17.5](#));
- Participant is lost to follow-up. All attempts to contact the participant must be documented;
- At the discretion of the treating investigator and following consultation with Study PI, for safety, behavioral, or administrative reasons;
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment or follow-up in the judgment of the investigator.

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5.13 Supportive Care, Prohibited and Concomitant Therapies/Medications

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator.

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the Electronic Health Record.

5.13.1 Prohibited therapies

The following are **prohibited** from **screening until the 30-day post-last-dose follow-up visit**:

- Other investigational agents other than pembrolizumab/ lenvatinib
- Anti-cancer medications, including chemotherapy or biologic therapy
 - **Exception:** neoadjuvant chemoradiotherapy as specified in this protocol.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have immunologic etiology. Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during the study.
 - **Exceptions:**
 - Inhaled steroids are allowed for management of asthma or seasonal allergies
 - Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
 - Participants are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
 - A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
- Supplements (including melatonin) and herbal medications

- Live vaccines

If any of the above agents are **deemed clinically necessary and no alternatives exist**, the participant must end study participation.

5.13.2 Other Considerations

Refer to [Appendix B](#) for contraception related guidance.

5.13.3 Supportive care

With the exception of therapies listed in [Section 5.12.1](#), participants should receive appropriate supportive care measures as deemed necessary by the treating investigator and per institutional guidelines. For participants receiving pembrolizumab (+ lenvatinib during window phase of therapy), suggested supportive care measures for the management of AEs are per Section 6.0.

6.0 PROTOCOL THERAPY DOSE MODIFICATION/ DELAY GUIDELINES

6.1 Dose Modifications and Delays for Carboplatin/Paclitaxel during Chemoradiation

Table 6.1.1 Carboplatin and Paclitaxel Dose Levels

	Starting Dose	Dose Level -1	Dose Level -2
Carboplatin	AUC 2	AUC 1.5	AUC 1
Paclitaxel	50 mg/m ²	40 mg/m ²	30 mg/m ²

Table 6.1.2 Dose Modification for Hematologic Toxicities

Hematologic Toxicity	Chemotherapy (carboplatin/paclitaxel)
≥ Grade 3 ANC	Interrupt chemotherapy* until ANC improves to ≤ Grade 2, then resume treatment at 1 dose level lower of carboplatin and paclitaxel
≥ Grade 3 platelets	Interrupt chemotherapy* until platelets improve to ≤ Grade 2, then resume treatment at 1 dose level lower of carboplatin and paclitaxel

Abbreviations: ANC = absolute neutrophil count.

* Investigator will defer to the radiation oncologist as to whether an interruption of the radiation therapy is also indicated.

Table 6.1.3 Dose Modification for Non-Hematologic Toxicities

Toxicity	Severity	Carboplatin/paclitaxel
Neurologic toxicity (peripheral neuropathy)	Grade 2	Reduce paclitaxel by 1 dose level for all subsequent doses. No change in carboplatin dosing.
	Grade 3	Permanently discontinue paclitaxel. No change in carboplatin dosing.
	Grade 4	Discontinue study treatment.
Hepatic dysfunction	Total bilirubin 1.5–3 × ULN AND AST/ALT ≤ 2.5 × ULN	Decrease paclitaxel by 1 dose level for all subsequent doses.

Toxicity	Severity	Carboplatin/paclitaxel
		No change in carboplatin dosing.
	Total bilirubin $\leq 1.5 \times \text{ULN}$ AND AST/ALT $2.5\text{--}10 \times \text{ULN}$	Decrease paclitaxel by 1 dose level for all subsequent doses. No change in carboplatin dosing.
	Total bilirubin $1.5\text{--}3 \times \text{ULN}$, AND AST/ALT $2.5\text{--}10 \times \text{ULN}$	Decrease paclitaxel by 2 dose levels for all subsequent doses. No change in carboplatin dosing.
	Total bilirubin $>3 \times \text{ULN}$ OR AST/ALT $>10 \times \text{ULN}$	Permanently discontinue paclitaxel. No change in carboplatin dosing.
IRR to paclitaxel	Grade 1-2	Stop infusion. Administer H1 and/or H2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pretreat before all subsequent doses.
	Grade 3-4	Stop infusion and permanently discontinue paclitaxel; may continue with carboplatin for remaining doses.
Nausea/vomiting	Grade 3 (≥ 6 episodes of vomiting in 24 hours) for 3 days or more, despite optimal medical management	Interrupt chemotherapy* until improves to $\leq$ Grade 2, then resume treatment. 1st incidence: Maintain dose level 2nd incidence +: Reduce by 1 dose level
	Grade 4	Discontinue study treatment.
Diarrhea	Grade 3 (≥ 7 stools per 24 hours over baseline) for 3 days or more, despite optimal medical management	Interrupt chemotherapy* until improves to $\leq$ Grade 2, then resume treatment.

Toxicity	Severity	Carboplatin/paclitaxel
		1st incidence: Maintain dose level 2nd incidence +: Reduce by 1 dose level
	Grade 4	Discontinue study treatment.
Other	Grade 3	Interrupt chemotherapy* until improves to $\leq$ grade 2, then resume treatment at 1 reduced dose level.
	Grade 4	Discontinue study treatment.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

* Investigator will defer to the radiation oncologist as to whether an interruption of the radiation therapy is also indicated.

6.2 Criteria to Initiate Protocol Therapy During the Window Period

Criteria to be met in order to initiate protocol therapy	Action if criterion to the LEFT is NOT met
1. Completed standard of care neoadjuvant chemoradiotherapy	Discontinue study participation if the participant was unable to complete chemotherapy due to unacceptable toxicities. Otherwise, consult the Study PI.
2. Completed 2-weeks of rest post-chemotherapy	Consult the Study PI.
3. Underwent endoscopic biopsy during Week 2 of window period	This will be considered a protocol deviation. Continue with protocol therapy.
4. ANC $\geq$ 1000/mm ³	Discontinue protocol therapy. Participant should go on to receive standard of care management as specified in the protocol post-end of window period.
5. Platelets $\geq$ 75,000/mm ³	
6. Serum total bilirubin $\leq$ 1.5 x ULN OR Direct bilirubin $\leq$ ULN if total bilirubin levels $>$ 1.5 x ULN	
7. AST $\leq$ 2.5 x ULN	
8. ALT $\leq$ 2.5 x ULN	

Criteria to be met in order to initiate protocol therapy	Action if criterion to the LEFT is NOT met
9. Creatinine $\leq 1.5 \times \text{ULN}$ OR <i>For patients with Creatinine $> 1.5 \times \text{ULN}$: creatinine clearance of $\geq 60 \text{ mL/min}$ per 24 hour urine test or the Cockcroft-Gault formula</i>	
10. Fully recovered from the acute toxic effects (except alopecia) of neoadjuvant chemoradiation therapy to $\leq$ Grade 1	
11. Absence of unrelated toxicity not present at baseline that might adversely affect participation/ administration of protocol therapy	

6.3 Dose Delay Guidelines for Pembrolizumab

- Toxicities will be graded using the NCI [CTCAE Version 5.0](#).
- Baseline values are from the last values obtained prior to treatment.
- Guidelines for dose delays related to pembrolizumab irAEs are stated in [Table 6.3.1](#).
- Guidelines for dose delays and management related to pembrolizumab infusion reactions are stated in [Table 6.3.2](#).

Table 6.3.1 Dose Delay Guidelines for Pembrolizumab irAEs

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 $\leq 10 \text{ mg}$ 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.

irAEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	- Monitor participants for signs and symptoms of pneumonitis - Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment - Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

irAEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	- Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). - Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. - Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold	- Initiate insulin replacement therapy for participants with T1DM - Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and	Monitor for signs and symptoms of hypophysitis (including

irAEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3 or 4	Withhold or permanently discontinue ^a	initiate hormonal replacements as clinically indicated	hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2	Continue	Treat with non-selective betablockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ^a		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) 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		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Intolerable/persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: GuillainBarré Syndrome, encephalitis		

irAEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; INR=International normalized ratio; irAE=immune-related adverse events; IV=intravenous; NCI=National Cancer Institute; RUQ=right upper quadrant; T1DM=type 1 diabetes mellitus; TBL=total bilirubin; ULN=upper limit of normal.

a. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Table 6.3.2 Dose Delay Guidelines and Management for Pembrolizumab Infusion Reactions

NCI CTCAE Grade of Pembrolizumab Infusion Reaction	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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop Infusion. 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr).	Participant may be premedicated 1.5 h ($\pm$ 30 minutes) prior to infusion of pembrolizumab with: - Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). - Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade of Pembrolizumab Infusion Reaction	Treatment	Premedication at Subsequent Dosing
	Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: - Epinephrine** - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=by mouth. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

6.4 Dose Delay/ Modification Guidelines for Lenvatinib

Table 6.4.1 Lenvatinib Dose Levels

	Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
Lenvatinib	20 mg/day	14 mg/day	10 mg/day	8 mg/day

Table 6.4.2 Dose Delay/Modification Guidelines for Lenvatinib AEs

Treatment-Related Toxicity ^{a,b}	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2^{c,d} or Grade 3^{e,f}		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg orally once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4^g: Discontinue Study Treatment		

- An interruption of study treatment for more than 28 days will require Sponsor's approval before treatment can be resumed.
- Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.
- Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
- Obese participants (BMI ≥ 30) with weight loss do not need to return to the baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they reach at least a BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.
- For asymptomatic laboratory abnormalities, such as Grade ≥ 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.
- For Grade 3 thromboembolic event, permanently discontinue lenvatinib.
- Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

6.4.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of $\leq 150/90$ mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's initial BP measurement is elevated (ie, systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP $\geq 160/100$ mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg occurs, the participant must resume the Day 15 evaluation until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the participant to capture the blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.

2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.
3. If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤ 150 mm Hg and diastolic BP ≤ 95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
 - o If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg recurs on the first dose reduction 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 an additional dose reduction only when systolic BP ≤ 150 mm Hg and diastolic BP ≤ 95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
 - o If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg recurs on the second dose reduction 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 third dose reduction only when systolic BP ≤ 150 mm Hg and diastolic BP ≤ 95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
 - o Additional dose reduction should be discussed with Sponsor.

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

1. Institute appropriate medical management
2. Discontinue study drug

6.4.2 Management of Proteinuria

Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing
2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) is required in the following situations:
 - o The first (initial) occurrence of $\geq 2+$ proteinuria on urine dipstick while on study drug
 - o A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
 - o When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is $\geq 2+$.

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥ 2.4 .

Grading of Proteinuria:

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. Management of lenvatinib administration will be based on the grade of proteinuria according to [Table 6.4.2](#).

Monitoring:

- Urine dipstick testing for participants with proteinuria $\geq 2+$ should be performed on D15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

6.4.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in [Table 6.4.2](#) should be followed.

6.4.4 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in [Table 6.4.2](#) should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

6.4.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

6.4.6 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in [Table 6.4.2](#) should be followed.

6.4.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = $([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

6.4.8 Management of Hemorrhage

Instructions in [Table 6.4.2](#) should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.4.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or $\geq$ Grade 4 fistula.

6.5 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q6W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following two scenarios:

- If an AE is identified during a treatment cycle (ie, after pembrolizumab dosing), only lenvatinib dose interruption is needed.

- If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

If the participant recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, T1DM) and other supportive care should be taken promptly.

Participants receiving the combination therapy (pembrolizumab + lenvatinib) must discontinue study therapy if any of the following occur:

1. ALT or AST $>5 \times$ ULN for more than 2 weeks
2. ALT or AST $>3 \times$ ULN and (TBL $>2 \times$ ULN or INR >1.5)
3. ALT or AST $>3 \times$ ULN with appearance of fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, and/or eosinophilia ($>5\%$).

7.0 ADVERSE EVENT LIST

7.1 Pembrolizumab and Lenvatinib

The expected toxicities for pembrolizumab and lenvatinib are as follows (asterisk signifies $\geq 10\%$; no asterisk signifies 1-10%, † signifies $< 1\%$ and ^ signifies unknown frequency):

	Pembrolizumab Per pembrolizumab IB (Edition 15, 2017)	Lenvatinib with Anti-PD-1 Antibody Per lenvatinib IB (Edition 15, 2018)
<i>Blood and lymphatic system disorders (includes Investigations)</i>	Anemia, neutropenia†, thrombocytopenia†, leukopenia†, lymphopenia†, eosinophilia†, hemolytic anemia†, immune thrombocytopenic purpura†	
<i>Cardiac</i>	Myocarditis†	
<i>Endocrine</i>	Hyperthyroidism, hypothyroidism, hypophysitis †, adrenal insufficiency †, thyroiditis†	
<i>Eye</i>	Uveitis †, dry eye †	
<i>Gastrointestinal</i>	Diarrhea*, nausea*, abdominal pain, vomiting, colitis, constipation, dry mouth, pancreatitis†, small intestinal perforation†	Diarrhea^
<i>General Disorders and Administration Site</i>	Fatigue*, asthenia, edema, pyrexia, influenza like illness, chills	Fatigue^
<i>Hepatobiliary</i>	Hepatitis†	
<i>Immune system</i>	Infusion related reactions, severe infusion reaction†, sarcoidosis†, solid organ transplant rejection^	
<i>Investigations (excluding hematologic)</i>	AST/ALT increased, blood alkaline phosphatase increased, blood creatinine increased, low sodium levels†, low potassium levels†, low calcium levels†, blood bilirubin increased†, amylase increased†, increased calcium†	Increased liver function tests^
<i>Metabolism and Nutrition</i>	Decreased appetite, type 1 diabetes mellitus †,	Decreased appetite^, hyponatremia^
<i>Musculoskeletal and Connective Tissue</i>	Arthralgia, back pain, myositis, musculoskeletal pain, arthritis, pain in extremity, tenosynovitis†	Arthralgia, rhabdomyolysis^, noncardiac chest pain^
<i>Nervous system</i>	Headache, dizziness, dysgeusia, epilepsy†, lethargy†, Guillian-Barré syndrome†, peripheral neuropathy†, myasthenic syndrome†, encephalitis†	
<i>Psychiatric disorders</i>	Insomnia†	
<i>Renal and urinary</i>	Nephritis †	Proteinuria^

	Pembrolizumab Per pembrolizumab IB (Edition 15, 2017)	Lenvatinib with Anti-PD-1 Antibody Per lenvatinib IB (Edition 15, 2018)
<i>Respiratory, Thoracic and Mediastinal</i>	Cough, pneumonitis, dyspnoea	
<i>Skin and Subcutaneous Tissue</i>	Pruritus*, rash*, vitiligo, dry skin, erythema, hair color changes†, eczema†, alopecia†, severe skin reactions† (includes Steven-Johnson Syndrome† and toxic epidermal necrolysis†)	Palmarplantar Erythrodysesthesia^, maculopapular rash^
<i>Vascular Disorders</i>	Hypertension†	Hypertension^

8.0 AGENT INFORMATION

8.1 Pembrolizumab

Please refer to the IB for a detailed description.

Pembrolizumab is FDA approved for advanced melanoma, metastatic NSCLC, recurrent or metastatic HNSCC, relapsed/refractory classical Hodgkin lymphoma, advance/metastatic urothelial carcinoma and unresectable/metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.

Pembrolizumab is not approved for this indication.

8.1.1 Other Names

KEYTRUDA®, MK-3475.

8.1.2 Description and Molecular Weight

<i>Type</i>	IgG4 kappa monoclonal
<i>Source:</i>	Humanized (from mouse)
<i>Target:</i>	PD-1 receptor
<i>Molecular weight:</i>	147 kDa

8.1.3 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

8.1.4 Pharmacokinetics

Half-life elimination: 26 days

8.1.5 Human Toxicity

See [Section 7.1](#).

8.1.6 Formulation

Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

Pembrolizumab Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0 mL (100mg).

8.1.7 Storage and Stability

Do not use pembrolizumab if **discoloration** is observed.

8.1.7.1 Non-diluted product

Store drug product between 2 °C -8°C and protected from light. **Do not shake or freeze the vials.**

Note: vials should be stored in the original box to ensure the drug product is protected from light.

Do not use pembrolizumab if discoloration is observed.

8.1.7.2 Reconstituted and diluted solutions

Do not freeze.

Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. The 4 hour countdown begins when the vial is pierced, and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion.

IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed.

8.1.8 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

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

8.1.9 Dose Calculation

400 mg fixed dose= 4 vials (100 mg/ 4mL) = 16 mL total

8.1.10 Preparation

1. Pembrolizumab infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab in the infusion solutions should be between 1 mg/mL and 10 mg/mL.
 - a. **Please note**, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.
2. Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline. The following infusion bag materials are compatible with pembrolizumab:
 - PVC plasticized with DEHP
 - Non-PVC (polyolefin)
 - EVA
 - PE lined polyolefin

*Contact Merck for materials not listed above
3. Pembrolizumab **SHOULD NOT BE MIXED WITH OTHER DILUENTS.**

4. Aseptic technique must be strictly observed throughout the preparation procedure
5. Use of a biosafety cabinet is preferred since no anti-microbial preservative is present in the product; however, it is not mandatory unless specified by site standard operating procedure.
6. Equilibrate required number of pembrolizumab vials to room temperature.
7. The preferred method of dose preparation is the volumetric method.
 - a. Reconstitution and administration of pembrolizumab that follows the parameters in this section is recommended, however if use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented:
 - i. Draw the required volume up to 4.0 mL (100 mg) of pembrolizumab from each vial
 - ii. Limit the number of punctures of each vial to one
 - b. For gravimetric preparation method using density of pembrolizumab solution, a value of 1.03 g/mL should be used
 - c. Merck does not support methods of preparation of non-Merck agents beyond what is stated in the product literature. Sites should reference the SmPCs or packaging inserts for preparation instructions
 - d. If the site procedures require use of spikes or other closed system transfer devices (CSTDs), please contact Merck for approval.
8. Choose a suitable infusion bag size so that the following conditions are met:
 - a. Concentration of pembrolizumab MK-3475 is between 1 mg/mL and 10 mg/mL
 - b. The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.
9. Calculate the volume of pembrolizumab and normal saline required to prepare the infusion (admixture) bag

$$\text{Volume of pembrolizumab (mL)} = \text{required dose amount (mg)} / 25 \text{ (mg/mL)}$$

$$\text{Volume of normal saline} = \text{total infusion volume} - \text{volume of pembrolizumab from above}$$

- a. If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of pembrolizumab would still fall within acceptable range.
- b. If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab to be added to the bag to prepare the infusion solution.

10. Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

Volume of pembrolizumab (mL) = required dose amount (mg) / 25 (mg/mL)

- a. **Note:** If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.
11. Add the required pembrolizumab into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.
 - a. **Discard any unused portion left** in the vial as the product contains no preservative.
12. For stability and storage of diluted product refer to [Section 8.1.7.2](#). **Do not freeze.**
13. If the infusion bag is excessively handled or shaken, particulates may form. If this occurs discard the bag and create a new bag taking care not to shake. Please contact Merck if particulates are noticed for further instructions. Be prepared to provide the following information:
 - IV bag manufacture, lot and expiry
 - Target volume of admixture solution in the IV bag (e.g. 100 mL, 200 mL etc.)
 - Amount of drug product (mL or mg) added to the bag
 - Drug product lot
 - Brief description of the nature of visible particles (color, shape, size, numbers etc.).
14. **All possible effort** should be made to **minimize agitation** of the drug product between the pharmacy and the clinic.

8.1.11 Administration

See [Section 5.6.1](#).

8.1.12 Temperature Excursions

1. To determine whether to report a temperature excursion, the temperature values should be rounded to whole numbers.
2. Rounding:
 - Decimal values from 0.1 to 0.4 round down to the nearest whole number (e.g., 8.3 = 8)
 - Decimal values from 0.5 to 0.9 round up to the nearest whole number (e.g., 8.7 = 9)
3. Compare the rounded values to the required temperature range to determine if there's an excursion.
4. All temperature excursions, however small, must be reported by the site to the Clinical Complaint Intake mailbox (clinical.complaints.intake@merck.com) for investigation within 1 business day using the Clinical Supply Complaint & GCP Inquiry Form (excel version).
 - a. All Clinical Supply stock that is subject to an investigation must be placed in quarantine and remain unavailable to dispense to patients until disposition has been determined.
5. Please note temperature excursions after drug product is prepared are out of scope of the clinical complaint process. Please contact Merck for further guidance.

8.1.13 Supplier

The agent will be supplied free of charge by Merck.

8.1.14 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

8.1.15 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures. **Prior** to the destruction of pembrolizumab, the DCC should be notified and an acknowledgement to proceed from the DCC should be received. Destruction will be documented in a drug accountability log.

8.2 Lenvatinib (as lenvatinib mesilate)

Please refer to the IB for a detailed description.

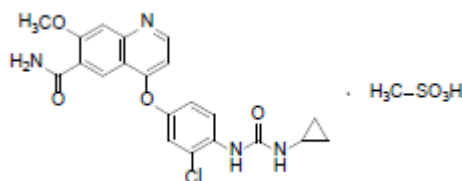
Lenvatinib has been FDA approved for the following indications: in February 2015 for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer; in May 2016 (in combination with everolimus) for the treatment of advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy; in August 2018 as the first-line treatment of patients for unresectable hepatocellular carcinoma (HCC). In September 2019, Lenvatinib was granted accelerated approved in combination with pembrolizumab for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

8.2.1 Other Names

E7080

8.2.2 Description and Molecular Weight

Structural formula:



Empirical formula: C₂₁H₁₉ClN₄O₄•CH₄O₃S

Molecular weight: 426.9

Chemical Name: 4-[3-Chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate

8.2.3 Mechanism of Action

Lenvatinib is a multiple receptor tyrosine kinase inhibitor with a potentially differentiated profile. It inhibits the 3 main vascular endothelial growth factor (VEGF) receptors (VEGFRs), VEGFR1, VEGFR2, and VEGFR3, as well as fibroblast growth factor (FGF) receptors (FGFRs), FGFR1, FGFR2, FGFR3, and FGFR4, platelet-derived growth factor receptor (PDGFR) α , c-kit, and the *RET* proto-oncogene, which play roles in tumor angiogenesis, tumor progression, and modification of tumor immunity.

8.2.4 Pharmacokinetics

Refer to the IB.

8.2.5 Human Toxicity

See [Section 7.1](#).

8.2.6 Formulation

Lenvatinib is available in capsules. The capsules contain the active drug (lenvatinib) along with commonly used compendial excipients (calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc).

8.2.7 Storage and Stability

Lenvatinib drug product should be stored in the original, labeled container at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F).

8.2.8 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

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

8.2.9 Administration

See [Section 5.6.2](#).

8.2.10 Supplier

The agent will be supplied free of charge by Merck.

8.2.11 Ordering

Each site should place a drug request order using the drug request form supplied by Merck or designee.

Merck or designee will deliver the study agent directly to the site due to stability issues.

8.2.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

8.2.13 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures. **Prior** to the destruction of lenvatinib, the DCC should be notified and an acknowledgement to proceed from the DCC should be received. Destruction will be documented in a drug accountability log.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Tumor Tissue Studies

Endoscopic biopsies will utilize standard 3-6 mm biopsy forceps with a goal of obtaining 4-6 biopsy specimens. As feasible, the same region of the tumor will be sampled.

An overview of collection, processing, and analysis details are shown in [Table 9.1](#).

Table 9.1 Tumor Tissue Studies Overview

Tissue Type	Timepoint of Collection	Receiving Lab	Downstream Analysis & Lab Performing Analysis
Frozen* Tissue	- Pre-chemotherapy – Snap-Frozen in OCT embedding media (2-3 biopsies) - Weeks 2 of window period - Snap-Frozen in OCT embedding media (2-3 biopsies) - For those without complete response: surgical resection specimen – Snap-Frozen in both liquid nitrogen as well as in OCT embedding media (5 blocks in total) - For those who did not have surgical resection: At time of surveillance visit – Snap-Frozen in OCT embedding media (2-3 biopsies)	COH Pathology Core	High Throughput Screening Core <u>Frozen Tissue:</u> PamChip PTK Array Kinome Profiling
			Molecular Pathology Core <u>Frozen Tissue:</u> Nanostring Gene Expression Profiling
Formalin fixed (FFPE)	- Pre-chemotherapy (1 biopsy as a research block and 1-2 biopsies as clinical specimens) OR submission of archival tissue obtained within 6 weeks prior to initiating chemoradiotherapy - Weeks 2 of window period (1 biopsy as a research block and 1-2 biopsies as clinical specimens) - For those without complete response: surgical resection specimen - For those who underwent surgical resection: at time of recurrence - For those who did not have surgical resection: At time of surveillance visit	COH Pathology Core	TGen <u>FFPE:</u> MHC-PepSeq
			Molecular Pathology Core <u>FFPE:</u> Nanostring Gene Expression Profiling

*For endoscopic biopsies dedicated for frozen tissue banking, the gastroenterologist should place all biopsy samples in a sterile saline container. Within 1 hour the pathology lab runner should transport this sterile saline container to the Histology Lab. The Histology Lab will subsequently call the Biorepository Core for pick-up for tissue processing. For surgical resection specimens, a portion of the tumor will be banked as frozen tissue as per standard COH Pathology Core

procedures. CRN should email a calendar invite of biopsy date to the designated Biorepository Core staff.

9.1.1 Distribution to laboratories for analysis

The COH Pathology core will distribute tissue to internal collaborators for downstream analysis.

9.2 Peripheral Blood Studies

Blood samples will be collected from an indwelling venous catheter or by venipuncture for the below stated analyses (see [Table 9.2](#)).

9.2.1 Timepoints of Collection and Tube Type

Timepoint of collection	Volume per Timepoint	Tube Type	Receiving & Processing Lab	Downstream Analysis & Lab Performing Analysis
- Baseline pre-chemoradiotherapy - Week 2 of window period - End of Week 8 of window period - For those who underwent surgical resection: at time of recurrence - For those who did not have surgical resection: At time of surveillance visit	21 mL	Green-top	COH APCF (Dr. Synold)	- ctDNA analysis – TGen Tardis assay - PBMC kinome profiling – High Throughput Screening Core - Cytokine profile on plasma - Dr. Synold - PBMC- immunoprofiling- COH Immuno-oncology Core - Anti-Drug Antibodies Testing – Dr. Synold
	5 mL	Purple-top		
	10 mL	Red-top		

9.2.2 APCF Notification, Blood Collection and Labeling

NOTE: It is **highly recommended** that non-Duarte sites arrange for a courier **prior to the participant's clinic visit** given the tight turnaround time for sample delivery to the COH APCF (Duarte Campus).

Notification to COH APCF of Pending Collection	Tube Type	Labeling and Collection Details	Post-collection Instructions
- Notify at least one day in advance) Send calendar invite via e-mail: Leslie Smith-Powell (Lsmith-Powell@coh.org) or Dauhlian Chi (dchi@coh.org)	Green-top Purple-top Red-top	- Label tubes with COH protocol #, subject ID, actual collection time in 24-hour format, institution (for CP sites), and timepoint of collection (e.g. pre-chemo, pre-immuno, post-immuno, F/U). - Timepoints of collection are stated in Section 9.2.1. - Blood samples will be collected from an indwelling venous catheter or by venipuncture - Invert tubes eight times after collection. Green-top and Purple-top tube(s): Immediately place the tubes on ice. Red-top tube(s): Keep red-top tubes at room temperature.	Promptly deliver the blood samples to the COH APCF, Shapiro room 1042 (Duarte Campus) for processing within 1-2 hours (± 30 minutes) of collection. Delivery temperature: - Green-top/purple-top tubes on ice or 4°C. - Red-top tube at room temperature. For non-Duarte sites courier deliveries should be made to the below address. All efforts should be made to deliver within the above specified window: Dr. Tim Synold Analytical Pharmacology Core Facility

Notification to COH APCF of Pending Collection	Tube Type	Labeling and Collection Details	Post-collection Instructions
			Shapiro 1042 City of Hope National Medical Center 1500 E. Duarte Road Duarte, CA 91010

9.2.3 Processing of samples at APCF

Keep blood samples on a rocker set at low speed to mimic circulation and avoid clot formation until processing.

Efforts should be made to process the samples **within 4 hours** of collection.

Tube Type	Processing Details	
Green-top	Plasma	- For plasma preparation use 14 mL whole blood from green-top tubes. - Centrifuge for 10 minutes at 1800 x g at 4 °C. - The resulting upper plasma layer from each tube will be drawn up sequentially into a sterile 5 mL syringe and pushed through a sterile 0.2/0.8 micron disposable filter. Save the plasma-depleted portion for isolation of PBMC (see below). - The filtered plasma will then be transferred in 500 µL aliquots into multiple appropriately-labeled Starstedt microfuge tubes. - To one aliquot, add 0.5 mL glycerol/0.02% sodium azide solution to dilute the plasma 50/50 v/v. Keep the diluted plasma sample at -20°C and do not freeze. - All the remaining plasma aliquots will be stored frozen at -80°C until use.
	Peripheral blood mononuclear cells (PBMC)	- Any blood remaining in the two green-top tubes used to prepare plasma above will be diluted 1:1 with Hank's Balanced Salt Solution (or equivalent) and combined with the whole blood from the unused green-top tube in a sterile 50 ml conical centrifuge tube. - PBMC will then be isolated per COH APCF procedures. - Isolated PBMC will be aliquoted and stored at -80°C/ liquid nitrogen until use.
Purple-top	Plasma	- Process per APCF Procedures. - Tubes should be de-identified prior to aliquoting and freezing (i.e. tubes should only contain protocol ID, study subject ID and timepoint of collection) - Plasma aliquots (~500 µL aliquots) will be stored frozen at -80°C until use.
Red-top	Serum	- If not already done so, allow the blood to clot for at least 1 hour at room temperature. - Process per COH APCF procedures. - Serum aliquots (~500 µL aliquots) will be stored frozen at -80°C until use.

9.2.4 Sample maintenance and distribution/shipping to laboratories

A sample manifest will be maintained by the PI or designee. Samples will be maintained at APCF until distribution to internal collaborators/external vendors. Samples will be batch shipped to non-COH vendors.

9.3 Stool Samples

9.3.1 Timepoints

- Baseline pre-chemotherapy
- Week 2 of window period
- End of Week 8 of window period

- For those who **underwent** surgical resection: at time of recurrence
- For those **who did not** have surgical resection: At time of surveillance visit

9.3.2 Collection, labeling, storage

1. Provide participant with a biospecimen bag, a stool collection bowl (toilet hat), a pre-labeled DNA/RNA Shield Fecal Collection Tube, and disposable gloves.
2. Instruct participant on proper collection.
3. Stool will be collected within 24-72 hours of collection, corresponding with the participant's next study visit.
4. **Remind the participant** at least 1-2 days in advance of the protocol visit to perform stool collection and store the sample at room temperature until the day of the scheduled clinic visit.
 - a. **Optional:** Participant may instead provide a stool sample at the clinic during the protocol visit provided they are reporting regular bowel movements.
5. **Labeling:** Label samples with COH protocol #, subject ID, institution (for CP sites), date of collection, and timepoint of collection (e.g. pre-chemo, pre-immuno, post-immuno, F/U).
6. **Promptly** store samples are at -20 °C until analysis.
7. **Community Practice Sites:**
 - a. Ship on ice at time of blood shipment to the COH Duarte campus
 - b. COH APCF will notify the study team to retrieve the sample



10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

Table 10.1 Study Activity Calendar – Screening and Chemoradiation Phase

Protocol Activity	Screening ^a	Chemoradiation + Pembrolizumab Phase					
		Protocol Therapy					
		D1 Week 1	D1 Week 2	D1 Week 3	D1 Week 4	D1 Week 5	D1 Week 6
Informed Consent ^b	X						
Medical History ^c	X						
Eligibility ^d	X						
Registration ^e	X						
Physical Exam	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Height	X						
Vital signs ^f	X	X	X	X	X	X	X
ECOG Status (Appx. A)	X	X	X	X	X	X	X
Con-med review ^g	X	X	X	X	X	X	X
AE Assessment ^h		X	X	X	X	X	X
12-lead EKG ⁱ	X						
Pregnancy ^k	X ^j						
Urinalysis including glucose & protein	X ^j						
CBC w/diff, plt & Serum chemistry ^l	X ^j	X	X	X	X	X	X
PT/INR/aPTT	X ^j						
Thyroid tests-TSH, T3, T4							
Correlative blood ^m	X ^j			X ^u			
Correlative tumor tissue ⁿ	X						
Endoscopic biopsy	X ^o						
Archival tumor tissue ^p	X ^o						
PET/CT ^q	X						
Carboplatin/paclitaxel ^r		X	X	X	X	X	
External beam radiation ^r		X					
Pembrolizumab ^r		X					
Participant orientation ^s	X						
Stool kit ^s	X						
Stool ^t	X ^j						

- a. *Screening* activities to occur within 6 weeks prior to initiation of the chemoradiotherapy phase except for clinical laboratory assessments.
- b. *Informed consent* process to be fully documented (see [Section 17.4](#)). Informed consent must occur prior to any research only (non-SOC) screening procedures.
- c. *Medical history* to include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
- d. *Eligibility criteria* are detailed in [Section 3.0](#).
- e. *Registration* into a COH clinical trial management system (CTMS).
- f. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.
- g. *Concurrent medications* and reason for administration to be documented in the EHR and eCRF from within 28 days prior to Day 1 of study participation and up to 90-days post-last dose of immunotherapy. See [Section 5.12.1](#) for concomitant medication restrictions and guidelines.
- h. *Adverse event (AE)* will be assessed using CTCAE v.5.0.
- i. If clinically indicated by history of cardiovascular disease.
- j. Within 14 days prior to Day 1 of study participation.
- k. *Women of childbearing potential only*: serum or urine pregnancy test.
- l. *Serum chemistry* panel to include: Albumin, Total Bilirubin, Total Calcium, Bicarbonate, Chloride, Creatinine, Glucose, Alkaline Phosphatase, Potassium, Total Protein, Sodium, ALT, AST, and BUN.
- m. *Correlative blood*: Green-top tubes (21 mL per timepoint) and purple-top (5 mL per timepoint) should be placed on ice. Red-top (10 mL per timepoint) should be kept at room temperature. See [Section 9.2](#). **NOTE**: APCF notification instructions of a pending collection at least one day before collection should occur per [Section 9.2.2](#).
- n. Research tumor tissue will be collected at time of standard of care endoscopic biopsy/ surgical resection. Refer to [Section 9.1](#) for tissue requirements.
- o. *Endoscopic biopsy (standard of care)* performed during endoscopic ultrasound to complete staging prior to initiating chemoradiotherapy. **NOTE**: Archival biopsies obtained at COH may fulfil this timepoint (i.e. obtained before informed consent).
- p. *If submitting archival tissue*: Submit FFPE upon study team request; should have been taken within 6 weeks prior to initiation of chemoradiotherapy
- q. *PET/CT (standard of care)*: base of skull to thigh for inclusion of neck, chest, abdomen, pelvis and any clinically indicated sites.
- r. Refer to [Section 5.0](#) for the treatment plan. Refer to [Section 6.3](#) for dose delay guidelines.
- s. Participants will be given instructions on how to collect stool samples and given a kit. Refer to [Section 9.3.2](#). See [Appendix E](#).
- t. *Correlative stool samples*: Can be obtained prior to planned clinic visit/ standard of care visit. Refer to [Section 9.3](#).
- u. Draw one purple-top tube only during week 3 of chemoradiation.

Table 10.2 Study Activity Calendar – Window Period and Surgery/Surveillance Follow Up

Protocol Activity	Window Period ^a								Assessments may be combined if windows for the two visits overlap				
	Rest Period		Protocol Therapy						End of Window & 90-days post-dose ^c	Surgical Resection ^d	Post-surgery F/U ^e	Surveillance ^f	Survival F/U ^g
	D1-D7 Week 1	D1-D7 Week 2	D1 Week 3 ^b	D1 Week 4	D1 Week 5	D1 Week 6	D1 Week 7	D1 Week 8					
Physical Exam	X		X	X	X	X	X	X	X				
Weight	X		X	X	X	X	X	X	X				
Height													
Vital signs ^h	X		X	X	X	X	X	X	X				
ECOG Status (Appx. A)	X		X	X	X	X	X	X	X				
Con-med review ⁱ	X		X	X	X	X	X	X	X				
AE Assessment ^j	X		X ^k	X ^k	X ^k	X ^k	X ^k	X ^k	X ^k		X	X	
12-lead EKG ^l													
Urinalysis including glucose & protein	X					X			X				
CBC w/diff, plt & Serum chemistry ^m	X		X	X	X	X	X	X	X				
Uric acid, phosphate, LDH													
PT/INR/aPTT													
Thyroid tests-TSH, T3, T4	X								X ⁿ				
Correlative blood ^o		X							X ⁿ		X ^p	X	
Correlative tumor tissue ^q		X								X	X ^p	X	
Endoscopic biopsy		X ^r										X	
Surgical resection										X			
PET/CT ^s								-----X-----			X	X ^s	
Criteria to initiate 1 st dose of protocol therapy ^b	X												
Pembrolizumab ^t			X										
Lenvatinib ^t					X								
Lenvatinib drug diary ^u					X								
Stool kit ^v		X						X			X ^p	X	
Reminder call for stool ^w		X						X					
Stool ^x		X							X ⁿ				
Survival ^g													X

- Window period (~ 8 weeks)* for all participants who end ~ 6 weeks of neoadjuvant chemoradiotherapy.
- Participants must meet criteria in [Section 6.2](#) to initiate pembrolizumab and lenvatinib on Day 1 Week 3 of the window period. Day 1 Week 3 is defined by the administration of lenvatinib.
- Safety visits for all patients who received protocol therapy. Safety visits to occur **(i)** end of Week 8 of the window period (+ 3 days) **AND (ii)** 90 (± 7) days post-last dose of protocol therapy or at initiation of a new anticancer

- therapy (whichever occurs first). Expedited reporting will occur during this period. Participants should be followed until resolution/ stabilization of reportable AEs.
- d. *Surgical resection (standard of care)*: Esophagectomy for participants **who did not** achieve complete response to occur end of Week 8 of the window period (+3 days).
 - e. *Post-surgery follow-up* (standard of care) for participants who received surgical resection to occur ~every 6 months ($\pm$ 14 days) for the 1st year, then ~every 6-12 months ($\pm$ 30 days) during the 2nd and 3rd year.
 - f. *Surveillance (standard of care)*: For participants who achieve complete response/ pursue non-operative management. The 1st surveillance biopsy to occur within 1 month of ending the window period, then every ~3 months from the 1st surveillance biopsy for the 1st year; every ~4 months for the 2nd year; every ~6 months for the 3rd year.
 - g. *Survival follow-up* for all study participants who received protocol therapy to occur bi-annually ($\pm$ 30 days) or as requested by the Study PI via medical record review, review of social security registry/ public records, and/or telephone call.
 - h. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.
 - i. *Concurrent medications* and reason for administration to be documented in the EHR and eCRF from within 28 days prior to Day 1 of study participation and up to 90-days post-last dose of immunotherapy. See [Section 5.12.1](#) for concomitant medication restrictions and guidelines.
 - j. *Adverse event (AE)* will be assessed using CTCAE v.5.0.
 - k. Active AE reporting will continue until the 90-days post-last dose of protocol therapy visit or until resolution/stabilization of any reportable AE occurring within the 90-days post-last dose of protocol therapy. **NOTE**: Refer to [Section 11.2](#) regarding routine reporting and [Section 14.6](#) for expedited reporting.
 - l. If clinically indicated by history of cardiovascular disease.
 - m. *Serum chemistry* panel to include: Albumin, Total Bilirubin, Total Calcium, Bicarbonate, Chloride, Creatinine, Glucose, Alkaline Phosphatase, Potassium, Total Protein, Sodium, ALT, AST, and BUN.
 - n. At end of Week 8 of window period (+ 3 days) visit only.
 - o. *Correlative blood*: Green-top tubes (21 mL per timepoint) and purple-top (5 mL per timepoint) should be placed on ice. Red-top (10 mL per timepoint) should be kept at room temperature. See [Section 9.2](#). **NOTE**: APCF notification instructions of a pending collection at least one day before collection should occur per [Section 9.2.2](#).
 - p. For participants who underwent surgical resection to occur only during recurrence.
 - q. Research tumor tissue will be collected at time of standard of care endoscopic biopsy/ surgical resection. Refer to [Section 9.1](#) for tissue requirements.
 - r. *Endoscopic biopsy (standard of care)* to occur during week 2 of the rest period.
 - s. *PET/CT (standard of care)*: base of skull to thigh for inclusion of neck, chest, abdomen, pelvis and any clinically indicated sites. **Timepoints of imaging are**: during Weeks 6-8 of the window period, then during post-surgery or during surveillance ~ every 6 months. Dedicated CT chest, abdomen, pelvis instead of PET/CT is acceptable during surveillance.
 - t. Refer to [Section 5.0](#) for the treatment plan. Refer to [Section 6.3](#) and [Section 6.4](#) for dose delay/modification guidelines.
 - u. *Lenvatinib drug diary*: will be given to the participant and will be reviewed for adherence. See [Appendix C](#).
 - v. Participants will be given instructions on how to collect stool samples and given a kit. Refer to [Section 9.3.2](#).
 - w. Study team to remind participant to collect stool via phone call; refer to [Section 9.3.2](#).
 - x. *Correlative stool samples*: Obtained prior to planned clinic visit/ standard of care visit. Refer to [Section 9.3](#).

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Primary Endpoints

Primary Objectives	Endpoints/ Measurements
To evaluate pathologic complete response rate (path CR) and complete clinical response rate (clinical CR) at 14 weeks after starting chemoradiotherapy.	Pathological CR defined as: - No residual cancer cells, including lymph nodes under pathologic examination of the surgically resected specimen and/or a Tumor Regression Score of 0 by the CAP Cancer Protocol for Esophageal Carcinoma [18]. Clinical CR defined as: No radiographic evidence of disease on PET/CT or CT imaging. - Residual FDG activity in the esophagus is permissible provided that endoscopic examination shows resolution of any visualized tumor masses and/or ulceration and no other tumors. - Mucosal irregularities are permissible provided that biopsies of esophageal areas previously preoccupied by tumor do not show any cancer cells under pathologic examination
To obtain initial data on the complete response rate for patients treated with CRT + pembrolizumab followed by pembrolizumab + lenvatinib	Pathological CR defined as: - No residual cancer cells, including lymph nodes under pathologic examination of the surgically resected specimen and/or a Tumor Regression Score of 0 by the CAP Cancer Protocol for Esophageal Carcinoma [18]. Clinical CR defined as: No radiographic evidence of disease on PET/CT or CT imaging. - Residual FDG activity in the esophagus is permissible provided that endoscopic examination shows resolution of any visualized tumor masses and/or ulceration and no other tumors. - Mucosal irregularities are permissible provided that biopsies of esophageal areas previously preoccupied by tumor do not show any cancer cells under pathologic examination

11.2 Secondary Endpoints

Secondary Objectives	Endpoints/ Measurements
To establish that pembrolizumab + lenvatinib will increase immune response via increased expression of the 18 gene pro-immune response signature measured using the Nanostring platform on tumor tissue biopsies.	Descriptive statistics will be compiled on circulating T cell profiles for each patient at pre- and post-therapeutic intervention with the combination Pembrolizumab and Lenvatinib. Repeated measures t-tests will be conducted to examine pre and post-intervention differences between baseline and post-treatment tumor tissue Nanostring expression profiling. Data will be screened for parametric statistical assumption and the alpha level for all statistical tests will be set at .05. The Bonferroni correction will be applied to adjust for potentially

Secondary Objectives	Endpoints/ Measurements
	inflated family wise error rates for multiple comparisons with the same sample
To assess safety and tolerability of pembrolizumab and lenvatinib in this patient population.	Unacceptable toxicities (defined below per CTCAE v 5.0) that are at least possibly related to immunotherapy occurring during Weeks 3-8 of the window period: Any toxicity that lasts > 7 days and prevent the participant from undergoing standard of care surgical resection Any toxicity that would, in the opinion of the Study PI, prevent continued administration of protocol therapy <i>Immune related toxicities</i> (except tumor flare reaction, allergic reaction and infusion related reaction) – Any ≥ Grade 3 irAE – Any Grade 2 irAE that requires steroid administration and tapering <i>Hematological</i> – Grade 3 neutropenia that lasts > 7 days – Grade 4 neutropenia inspite of growth factor support – Grade 3/4 febrile neutropenia that requires a dose adjustment – Grade 3/4 thrombocytopenia with bleeding or requiring platelet transfusion – Other Grade 3/4 hematologic toxicity that does not resolve to ≤ Grade 1 within 72 hours despite supportive care <i>Non-hematological (non-irAEs)</i> Any ≥ Grade 3 non-hematological toxicity with the following exceptions: ○ Grade 3 fatigue that resolves within 7 days with supportive measures to ≤ Grade 2/ baseline ○ Grade 3 nausea, vomiting controlled with supportive measures and resolves within 72 hours to ≤ Grade 2 ≥ Grade 3 electrolyte abnormality that lasts < 72 hours that is not clinically complicated, and resolves spontaneously or responds to supportive care care to ≤ Grade 2

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a Phase 2 trial with a Safety Lead-in to evaluate neoadjuvant protocol therapy (pembrolizumab and lenvatinib) in patients with non-metastatic esophageal squamous cell and adenocarcinomas of the esophagus and gastroesophageal junction during the window period.

12.1.1 Primary Objectives:

To evaluate pathologic complete response rate (path CR) and/or complete clinical response rate (clinical CR) at 14 weeks after starting protocol chemoradiotherapy. Patients will be considered a “complete response” if there is a documented pCR or if there is a clinical CR and the patient pursues non-surgical management. The latter is expected only for squamous cell carcinomas, which should comprise approximately 25% of the patient population, and the clinical CR requires a negative biopsy. As a result, we can use the Phase 3 CROSS trial results as general benchmark.

Specifically, if after 13 patients are treated, fewer than 4 complete responders are observed, the study would be considered discouraging and accrual would stop. If the true CR rate is 50%, which is considered promising, the probability of 3 or fewer responders out of 13 patients is less than 5%.

If at least 4/13 patients experience a complete response (~31%), the study will continue until a total of 24 patients are treated. With 24 patients, the complete response rate can be estimated with a standard error of 10% or less. Subset analysis on adenocarcinomas and squamous will be conducted as part of the exploratory analysis.

Safety Lead-in: While acceptable toxicities have been established in the Phase 1 study with the combination of lenvatinib and pembrolizumab that is being utilized in Phase 2/3 studies, the initial treatment of patients within the context of this trial still warrants a careful review of toxicity. The Safety Lead-in will utilize a 3-at-risk design; the study will only permit 3 patients to be at risk for unacceptable toxicities at any one time during the Safety Lead-in. Unacceptable toxicities are defined in [Section 11.2](#). Patients evaluable for unacceptable toxicities during the Safety Lead-in are defined in [Section 12.2](#). If ≤ 1 of the first 6 patients experience unacceptable toxicities during the window period, protocol therapy will be considered tolerable. If ≥ 2 of the first 6 patients experience unacceptable toxicities during the window period, protocol therapy will be deemed intolerable and a study hold will be placed for re-evaluation of the proposed lenvatinib starting dose, with re-opening of accrual requiring DSMC approval.

12.1.2 Secondary Objectives:

To establish that the combination of pembrolizumab and lenvatinib in the neoadjuvant setting in the study population will lead to an increase in immune-mediated tumor cytotoxicity via an increase in tumor infiltrating and circulating cytotoxic T cells within the tumor microenvironment post- chemoradiotherapy.

Each patient will serve as their own control, and tumor cytotoxic T cell infiltration will be compared between the post-chemoradiation biopsy (pre-pembrolizumab/lenvatinib) and post-treatment (definitive surgery or follow up biopsies if clinical CR) via increased expression of the 18 gene pro-immune response signature measured using the Nanostring platform on tumor tissue biopsies.

A positive biological signal combined with acceptable safety and tolerability and primary endpoints (path CR and clinical CR) are sought for a clear indication of promise of this combination. With 13 patients,

there is 80% power to detect a difference of 73% of the standard deviation of the difference (pre-post), with a type I error of 5% (one-sided). If the study continues to 24 patients, the same power exists to detect a difference of 52% of the standard deviation of the difference. We will also compare the baseline value between complete responders and non-responders. If we assume 50% complete responders (12 vs 12), there is 90% power to detect a difference of 1.25 x standard deviation in the signature score with a type I error of 5% (one sided). If the complete response rate is 33%, with 8/24 responders, the power is reduced to 87% for the same effect.

12.1.3 Exploratory Objectives:

To identify through an integrated genomic sequencing approach (MHC-PepSeq) the presence of tumor mutations able to elicit neo-antigen-specific immunity in this population expected to be predominated by MSS tumors. To correlate temporal variations in ctDNA representing immunogenic and non-immunogenic mutations as pharmacodynamic immune markers. To correlate diversity in the gut microbiome with path CR and clinical CR in this study population.

12.2 Evaluable Participants and Participant Replacement

- **Evaluable for toxicity:** All patients who receive at least one dose of immunotherapy will be evaluable for toxicity.
- **Evaluable for Unacceptable Toxicity During Safety Lead-in:**
Participants will be considered to be evaluable for unacceptable toxicity if:
 1. They receive at least 1 of 2 pembrolizumab doses **AND** at least 75% of the planned lenvatinib during the window period; **OR**
 2. They experience an unacceptable toxicity during Weeks 3-8 of the window period ([Section 11.2](#)).Participants inevaluable for unacceptable toxicity will be replaced.
- **Evaluable for Response:** Participants will be considered evaluable for response if they are confirmed eligible, and receive any of the planned neoadjuvant protocol therapy. Patients not completing neoadjuvant protocol therapy for any reason or having not obtained an end of neoadjuvant therapy tumor specimen will be classified as non-path CRs.

12.3 Sample Size, Accrual Rate and Study Duration

- **Total accrual:** The total number of participants treated (combining safety lead-in and Phase 2 cohorts) is expected to be 24 patients.
- **Accrual rate and Study Duration:** Assuming 1-2 patients are enrolled each month, accrual is expected to be completed in 24 months. Participant duration is planned for ~3 1/2 years. Study duration is planned for ~6 years.

12.4 Stopping Rules

If at any point, any of the following events occur, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee (DSMC) will be mandated:

- Any treatment related death

Patient accrual will not resume until approved by the regulatory committees, including DSMC.

12.5 Toxicity Monitoring after Safety Lead-in

Close and continuous monitoring for toxicity will occur throughout the study duration per institutional standards. The City of Hope Data Safety Monitoring Committee (DSMC) will review the toxicity data on this study quarterly. The expected rate of “unacceptable toxicity” as defined in [Section 11.2](#) should not be $\geq 33\%$. The stopping rule for “unacceptable toxicity” will be assessed after at least 6 patients are treated at the dose deemed tolerable for Phase 2 evaluation and at the interim analysis of 13 patients. If “unacceptable toxicity” events occur in $\geq 33\%$ of patients treated at the quarterly review or any time after the initial safety evaluation (lead-in), accrual will be halted and a full review of these events will be performed by the City of Hope DSMC. Patient accrual will not resume until approved by the DSMC to do so. These rules are in addition to the quarterly review of all toxicities submitted to the City of Hope DSMC. Patients with ongoing toxicity will be followed until resolution or stability.

12.6 Statistical Analysis Plan

Patient demographics and baseline disease/prior treatment characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as number, mean, standard deviation, standard error, median (range) etc. will be provided. For categorical variables, patient counts and percentages will be provided.

All patients evaluable for toxicity will be included in the toxicity analysis. Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, time of onset, duration, probable association with the study treatment and reversibility or outcome.

For pathological CR and clinical CR, all patients evaluable for response will be included in the analysis. Pathological CR rate and clinical CR rate will be estimated by the proportion of patients achieving pathological CR and clinical CR, along with the 95% exact binomial confidence interval. DFS and OS will be determined using the Kaplan-Meier method.

Descriptive statistics will be used to summarize the gene expression profile in tissue/blood. Changes in these measures during and after treatment (when measured) will also be summarized by descriptive statistics and tables/plots. Various statistical analyses will be used to explore the association between these gene expression measures (at different time points and the changes over time) with clinical outcomes. For the exploratory correlation of these endpoints with response, analyses comparing groups of participants defined by response may be conducted by two-sample t-test or Wilcoxon rank sum test. For the exploratory correlation of these endpoints with survival outcomes, survival analysis techniques such as Log rank test will be considered. All these analyses are exploratory in nature and are intended to generate hypotheses that may be validated in larger studies; no multiple comparison adjustments will be made in these exploratory analyses.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in [Section 13.2](#), and will be submitted according to the timelines indicated in [Table 13.3](#).

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	During Weeks 3-8 of window period: Within 7 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS REPORTING

The research team is responsible for classifying AEs and UPs as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e. grade), expectedness, and attribution of all adverse events as applicable per the [City of Hope Clinical Research Adverse Event and Unanticipated Problem policy](#). Adverse events will be characterized using the descriptions and grading scales found in version 5.0 of the NCI CTCAE. A copy of the scale can be found at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated** – The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely** – The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible** – The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable** – The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite** – The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 Reporting of Adverse Events

14.2.1 Routine Recording of Non-Serious Adverse Events

Routine recording of all grades of adverse events will occur via data entry into the study eCRF. Collection of adverse events will begin after the patient is given the study treatment or any study related procedures and will continue until ending study participation. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

14.2.2 Expedited Reporting Requirements of SAEs and UPs to the COH Regulatory Committees

Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved [City of Hope Clinical Research Adverse Event and Unanticipated Problem policy](#). Reporting of SAEs will begin with the patient is given the study treatment or any study related procedures, and must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

14.3 Adverse Events of Special Interest (AESIs)

14.3.1 Immune-related AEs

An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

14.4 Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥ 2.5 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 AE(s) is associated with ("results from") the overdose of a pembrolizumab, the AE(s) is reported as a SAE, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as "accidental or intentional overdose without adverse effect."

For lenvatinib and overdose is defined as any amount over the protocol-specified dose.

14.5 Pregnancy and Breastfeeding

Although pregnancy and breastfeeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or breastfeeding that occurs during the trial; See [Table 14.6](#).

Efforts must be made by the investigator to follow the outcome of pregnancy outcome per institutional policies.

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; weight and length of child, Apgar scores (with an explanation of score <10), and congenital abnormalities. If the new-born is healthy additional follow-up is not necessary.

14.6 Abnormal liver function tests

Liver function tests that meet the following criteria as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing must be reported expeditiously to Merck.

- An elevated AST or ALT $\geq 3X$ ULN **in combination with** total bilirubin $\geq 2X$ ULN **and** an alkaline phosphatase lab value that is $< 2X$ ULN.

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.

14.7 Expedited Reporting

The table below indicates what events to report expeditiously ([Table 14.6](#)).

Table 14.6 Expedited Reporting Guidelines

Time point	What to report to Merck
From signing of the consent to study completion	• All UPs
Day 1 of chemoradiotherapy phase to Day 1 of protocol therapy with pembrolizumab/ lenvatinib	• Pregnancy and lactation
From Day 1 Week 3 of window period through 90 days post-last dose of immunotherapy, or end of Week 8 of window period if the subject initiates new anticancer therapy, whichever is earlier All reportable events will require follow up until stabilization or resolution per the agreement of the Study PI.	• All SAEs regardless of relationship to protocol therapy • All AEs that meet the definition of a UP • All AESIs (Section 14.2) • Overdose of either agent (Section 14.3) • Pregnancies and breastfeeding (Section 14.4) • Abnormal liver function tests (Section 14.5)
From Day 1 Week 3 of window period up to 120 days post-last immunotherapy dose	• Pregnancies and lactation
Post Safety follow-up to end of study participation	• All SAEs that are considered probably or definitely related to pembrolizumab or lenvatinib.

14.8 Reporting to Merck

The Study PI (or designee) will:

- Report the following to Merck per the guidelines provided below ([Table 14.7](#)).
 - **Merck Global Safety** facsimile number 215 993-1220 (Attn: Worldwide Product Safety).
- Assist Merck in investigating any SAE and will provide any follow-up information reasonably requested by Merck.

Table 14.7. Timeframes for Reporting to Merck

Type of Report	Reporting Timeframes to Merck
Pregnancy/ breastfeeding	Within 24 hours of being aware of the event Use industry partner pregnancy reporting form if available

Type of Report	Reporting Timeframes to Merck
SAE (includes AEs, overdose/misuse, abnormal liver function tests)	Within 24 hours of being aware of the event via a MedWatch 3500A form.
Any event that meets expedited FDA reporting requirements	Promptly forward the MedWatch 3500A form to Merck (via OIRA)
Aggregate FDA reports	Forward to Merck (via COH OIRA) copies of initial/annual/final FDA IND submissions.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the [Clinical Research Protocol Deviation policy](#).

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Quality Assurance

Clinical site auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. This trial will be audited by the City

of Hope Office for Safety and Data Quality. Details of clinical site auditing are documented in the [City of Hope Institutional Data and Safety Monitoring Plan \(DSMP\)](#).

16.5 Risk Determination

This is a moderate risk study, as defined in the [City of Hope Institutional DSMP](#). This determination was made because the study is an investigator-initiated Phase II study that is IND exempt.

16.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the [City of Hope Institutional DSMP](#)). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
 - Title 21 Part 11 – Electronic Records; Electronic Signatures
 - Title 21 Part 50 – Protection of Human Subjects
 - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
 - Title 21 Part 56 – Institutional Review Boards
 - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
 - Title 21 Part 312 – Investigational New Drug Application
 - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
 - Health Insurance Portability and Accountability Act of 1996
 - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable, NIH policies and procedures
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the study drugs may potentially affect the developing fetus.

17.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study since safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

The incidence of esophagus or esophagus and gastroesophageal junction cancer is rare in the pediatric population.

17.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant 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.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens with a limited data set will be provided to collaborating laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved with some clinical information and potentially PHI attached or (b) discarded.

Any coded specimens sent to external collaborators will be discarded upon study completion.

17.9 Conflict of Interest

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 (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Pembrolizumab and lenvatinib will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and Merck. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the [U.S. Public Law 110-85](#) (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto [ClinicalTrials.gov](#). Results will be reported on [ClinicalTrials.gov](#) generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

18.0 REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer Statistics, 2017*. CA Cancer J Clin, 2017. **67**(1): p. 7-30.
2. *National Comprehensive Cancer Network: Esophageal and Esophagogastric Junction Cancers (Version 1.2017)*. 2017 March 24, 2017]; Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#esophageal.
3. van Hagen, P., et al., *Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer*. New England Journal of Medicine, 2012. **366**(22): p. 2074-2084.
4. Bedenne, L., et al., *Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102*. J Clin Oncol, 2007. **25**(10): p. 1160-8.
5. Vincent, J., et al., *Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: Chemoradiation followed by surgery versus chemoradiation alone*. European Journal of Cancer, 2015. **51**(13): p. 1683-1693.
6. Sullivan, K.E., E.T. Hurley, and J.P. Hurley, *Understanding Complete Pathologic Response in Oesophageal Cancer: Implications for Management and Survival*. Gastroenterology Research and Practice, 2015. **2015**: p. 9.
7. Osipov, A., et al., *Impact of chemoradiotherapy on PD1/PDL1 expression and clinical outcomes in gastroesophageal cancers*. Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 4031-4031.
8. Dovedi, S.J., et al., *Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade*. Cancer Research, 2014. **74**(19): p. 5458-5468.
9. Twyman-Saint Victor, C., et al., *Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer*. Nature, 2015. **520**(7547): p. 373-377.
10. Park, S.S., et al., *PD-1 Restrains Radiotherapy-Induced Abscopal Effect*. Cancer Immunol Res, 2015.
11. Ohigashi, Y., et al., *Clinical Significance of Programmed Death-1 Ligand-1 and Programmed Death-1 Ligand-2 Expression in Human Esophageal Cancer*. Clinical Cancer Research, 2005. **11**(8): p. 2947-2953.
12. Derks, S., et al., *Epithelial PD-L2 Expression Marks Barrett's Esophagus and Esophageal Adenocarcinoma*. Cancer Immunology Research, 2015. **3**(10): p. 1123-1129.
13. Makker, V., et al., *994OLenvatinib (LEN) and pembrolizumab (PEMBRO) in advanced endometrial cancer (EC)*. Annals of Oncology, 2019. **30**(Supplement_5).
14. Kelly, R.J., et al., *Neoadjuvant nivolumab plus concurrent chemoradiation in stage II/III esophageal/gastroesophageal junction cancer*. Journal of Clinical Oncology, 2019. **37**(4_suppl): p. 142-142.
15. Ryan, R., et al., *Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer*. Histopathology, 2005. **47**(2): p. 141-6.
16. Chirieac, L.R., et al., *Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation*. Cancer, 2005. **103**(7): p. 1347-55.
17. Gopalakrishnan V., et al., *Association of diversity and composition of the gut microbiome with differential responses to PD-1 based therapy in patients with metastatic melanoma (suppl 7S; abstract 2)*. J Clin Oncol 35 2017.
18. Washington K., Berlin J., and Branton P., *Protocol for the examination of specimens from patients with carcinoma of the esophagus*. College of American Pathologists Cancer Protocols 2016.

19. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol, 1982. 5(6): p. 649-55.

APPENDIX A: ECOG PERFORMANCE STATUS

ECOG Performance Scale [19]	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: CONTRACEPTION GUIDELINES

Pembrolizumab and lenvatinib may have adverse effects on a fetus in uterus. Furthermore, it is not known if pembrolizumab has 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:

- 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**
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; **OR**
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.

Single method (one of the following is acceptable): Combination method (requires use of two of the following):

- | | |
|--|---|
| <ul style="list-style-type: none"> ○ intrauterine device (IUD) ○ vasectomy of a female subject's male partner ○ contraceptive rod implanted into the skin | <ul style="list-style-type: none"> ○ 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.

APPENDIX C-1: LENVATINIB PATIENT DRUG DIARY INSTRUCTIONS

Subject ID#:	Patient Initials (F, M, L):
Institution:	Start date: _____
☐ Safety Lead-in	☐ Phase 2

**Remember to bring this diary, all tablet bottles, and any unused tablets to each clinic visit.
Call your study doctor or nurse immediately if you are having any new or worsening side effects.**

Study drug Instructions – When and How:

- Take lenvatinib **once a day** with a full glass of water
- Swallow tablets whole; do not chew them or crush them unless given specific instructions by your physician or research nurse
- Do not skip any doses

What if I miss a scheduled dose?

- Take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time

What if I vomit a dose?

- If you vomit your tablets, write this down in your patient diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- **Write down your side effects in this diary.**
- Your dose may be adjusted based on your side effects
- Keep your study drug in the original container until you take it.
- Do NOT throw away empty study drug bottles or unused tablets.
- Bring this diary, all study drug bottles, and any unused tablets to each clinic visit.

Study Contact Information		
<u>Study Doctor</u> Phone: Name:	<u>Study Nurse</u> Phone: Name:	<u>Backup Study Nurse</u> Phone: Name:

APPENDIX C-2: LENVATINIB PATIENT DRUG DIARY

Subject ID#:	Patient Initials (F, M, L):
Institution:	Start date: _____
☐ Safety Lead-in ☐ Phase 2	

Call your study doctor or nurse immediately if you are having any new or worsening side effects. Your study doctor or nurse will tell you what to do.

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week _____				# of tablets to take: AM/PM: _____	
Day	Week Day	Date	Time	# of tablets taken (Write down below)	Comments <i>Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)</i>
1			____:____AM/PM		
2			____:____AM/PM		
3			____:____AM/PM		
4			____:____AM/PM		
5			____:____AM/PM		
6			____:____AM/PM		
7			____:____AM/PM		

Participant/ Caregiver Signature (please sign when submitting your diary)

Date:

____/____/____

Subject ID#:	Patient Initials (F, M, L):
Institution:	Start date: _____
☐ Safety Lead-in	☐ Phase 2

Call your study doctor or nurse immediately if you are having any new or worsening side effects. Your study doctor or nurse will tell you what to do.

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week _____				# of tablets to take: AM/PM: _____	
Day	Week Day	Date	Time	# of tablets taken (Write down below)	Comments Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)
8			__:__ AM/PM		
9			__:__ AM/PM		
10			__:__ AM/PM		
11			__:__ AM/PM		
12			__:__ AM/PM		
13			__:__ AM/PM		
14			__:__ AM/PM		

Participant/ Caregiver Signature (please sign when submitting your diary)

Date:

____/____/____

Subject ID#:	Patient Initials (F, M, L):
Institution:	Start date: _____
☐ Safety Lead-in ☐ Phase 2	

Call your study doctor or nurse immediately if you are having any new or worsening side effects. Your study doctor or nurse will tell you what to do.

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week _____				# of tablets to take: AM/PM: _____	
Day	Week Day	Date	Time	# of tablets taken (Write down below)	Comments Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)
15			____:____ AM/PM		
16			____:____ AM/PM		
17			____:____ AM/PM		
18			____:____ AM/PM		
19			____:____ AM/PM		
20			____:____ AM/PM		
21			____:____ AM/PM		

Participant/ Caregiver Signature (please sign when submitting your diary)

Date:

____/____/____

Study Team ONLY: # of Study Drug Bottles Returned: _____ # of tablets returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of tablets returned), please reconcile (initials & date): _____

Subject ID#:	Patient Initials (F, M, L):
Institution:	Start date: _____
☐ Safety Lead-in ☐ Phase 2	

Call your study doctor or nurse immediately if you are having any new or worsening side effects. Your study doctor or nurse will tell you what to do.

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week _____				# of tablets to take: AM/PM: _____	
Day	Week Day	Date	Time	# of tablets taken (Write down below)	Comments Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)
22			__:__ AM/PM		
23			__:__ AM/PM		
24			__:__ AM/PM		
25			__:__ AM/PM		
26			__:__ AM/PM		
27			__:__ AM/PM		
28			__:__ AM/PM		

Participant/ Caregiver Signature (please sign when submitting your diary)

Date:

____/____/____

Study Team ONLY: # of Study Drug Bottles Returned: _____ # of tablets returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of tablets returned), please reconcile (initials & date): _____

APPENDIX D: GUIDANCE FOR PATIENTS UNABLE TO SWALLOW WHOLE LENVATINIB TABLETS

Guidance for Subjects who cannot swallow intact tablets

The preferred method is dissolving tablets in water for those who can drink without difficulty. Crushing a tablet and putting the powder in a medium such as applesauce or water should be used if the patient requires a medium to swallow.

Preparation for dissolving

- Add capsule to a tablespoon of water or apple juice in a small glass to produce a suspension and let it sit for 10 minutes
- Stir for at least 3 minutes. Drink the mixture.
- After drinking, add the same amount of water or apple juice (one tablespoon) to the glass. Swirl the contents of the glass a few times and swallow the additional liquid.

APPENDIX E: FECAL SAMPLE COLLECTION INSTRUCTIONS (TO BE INCLUDED IN FECAL COLLECTION KIT)

You have been provided a Fecal Swab Collection kit.

The collection kit includes the following items:

1. Disposable Gloves
2. A stool collection bowl (toilet hat), as pictured below.



3. A bio-specimen bag
4. A pre-labeled DNA/RNA Shield Fecal Collection Tube, as pictured below. The tube has already been labeled with your assigned subject ID. Please DO NOT write your name on the label.



5.

In order to ensure the best results, please follow the instructions below.

You will need to collect **four different** stool samples during the treatment cycle:

1. The first stool sample is to be collected within 14 days of starting chemoradiotherapy.
2. The second stool sample is to be collected during Week 2 after completing chemoradiotherapy.
3. The third stool sample is to be collected end of Week 8 after completing chemoradiotherapy.
4. The fourth stool sample is to be collected at the time of your surgery; if you did not have surgery, then the fourth stool sample will be collected at the time of your next surveillance follow-up visit.

To Collect a Stool Specimen:

1. Raise the toilet seat and place the stool collection container (toilet hat) on the back of toilet bowl. Place the toilet seat down.
2. Pass stool into the stool collection container. Do not urinate into the container.
3. Put the provided disposable gloves on before collecting the stool sample. Use the scoop on the lid of the tube to collect a pea size amount of stool. Do not touch the swab on the sides of the collection bowl or on any other surface. Carefully re-insert the scoop into the tube, screw to close and then shake to homogenize.
4. Write the date and time of collection on the label that is affixed to the tube. **DO NOT** write your name on the tube.
5. Dump the remaining stool in the toilet and flush. The stool collection bowl and the disposable gloves may be disposed in the regular trash. Wash your hands thoroughly with soap and water.
6. Store the CultureSwab tube in the bio-specimen bag at room temperature.
7. Return the sample to the study team within 24-72 hours of collection. This should correspond with your next study visit. Sample can be transported in the car without need for ice packs.

IMPORTANT: If for some reason you cannot make your scheduled appointment within 72 hours of the fecal collection, please contact your research team to make arrangements for return of the sample.

If you have any questions please call your research team.

Thank you for your participation!