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# PHASE I/II TRIAL OF PERIOPERATIVE AVELUMAB IN COMBINATION WITH CHEMORADIATION IN THE TREATMENT OF STAGE II/III RESECTABLE ESOPHAGEAL AND GASTROESOPHAGEAL JUNCTION CANCER

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# PROTOCOL SYNOPSIS

## Title of study:

Phase I/II Trial of Avelumab In Combination With Chemoradiation In The Treatment Of Stage II/III Resectable Esophageal and Gastroesophageal Junction Cancer.

**Study Phase:** I/II

## Background:

Neoadjuvant chemoradiation is part of the standard of care for patients with stage II and III resectable esophageal and gastroesophageal junction (E/GEJ) cancer. This approach is based on the results of a large randomized clinical trial (CROSS) that demonstrated superior survival in patients receiving neoadjuvant chemoradiotherapy followed by surgical resection compared to patients treated with surgery alone. Pathological complete response at the time of resection is strongly linked to better survival. However, with current strategies pathological complete response is achieved only in a minority (29%) of patients. Remaining patients, especially those with positive lymph nodes at the time of the resection, are at significant risk for recurrences. Five-year survival rate for these patients is only 37%, and overall survival is as low as 9 months for those with persistent lymph node disease. Among patients who develop recurrent disease, most present with distant metastases outside of the radiation field. This is not surprising since the accepted treatment paradigm for this disease does not target possible disseminated microscopic systemic disease. Hence, novel strategies are needed to improve outcomes of these patients. We propose conducting a phase I/II clinical trial evaluating a role of immune checkpoint inhibitor in combination with chemoradiotherapy and post-operatively in the management of resectable esophageal cancer.

## Study Rationale:

1. A number of preclinical and clinical studies demonstrated synergism between radiation and immunotherapy, suggesting that combining these approaches can enhance anti-tumor activity and increase treatment efficacy.
2. Immune checkpoint inhibitors have demonstrated promising activity in a subset of patients with metastatic esophageal and gastric cancers. Moving these agents into neoadjuvant setting may increase the cure rate of this disease compared to the standard approach.
3. Current neoadjuvant therapy does not target any potential microscopic disease outside of the radiation field since chemotherapy serves primarily as a radiation sensitizer. Immunotherapy treatment will target both local and systemic disease.

## Hypothesis:

We hypothesize that co-administration of avelumab with chemoradiation will be well tolerated and will increase pathological complete response rate in resected tumor specimens. We hypothesize that avelumab treatment will also decrease the rates of disease recurrence.

**Study Design:**

This is a 2 part Phase I/II clinical trial evaluating the safety, tolerability and efficacy of avelumab in combination with chemoradiation in patients with resectable esophageal and GEJ (E/GEJ) cancer.

Part 1: This is the run-in phase of the trial. This portion will determine the safety and tolerability of avelumab in combination with chemoradiotherapy in 6 patients. The proposed combination will be considered as safe if dose limiting toxicities are observed in at most 1 patient.

Part 2: This is a Phase 2 portion of the trial, which will evaluate the efficacy of the proposed treatment regimen in patients with stage II/III resectable E/GEJ cancer.

**Objectives:**

Primary: Evaluate the safety of avelumab in combination with chemoradiation in patients with resectable esophageal cancer receiving perioperative therapy.

Secondary: Obtain efficacy data and further safety data of the proposed drug combination in this patient population.

Exploratory objectives:

The translational focus of the study will evaluate changes in tumor microenvironment that occur in response to radiation and immunotherapy.

**Endpoints:**

Part 1:

Primary endpoint:

1. Establish safety and tolerability of the proposed treatment.

Part 2:

Primary Endpoint:

1. Pathological complete response rate.

Secondary Endpoint:

1. Safety and tolerability.
2. Disease free survival.
3. Incidence of surgical complications.
4. Rate of R0 resection.

**Number of centers & patients:**

One center.

Part 1: total of 6 eligible patients will be accrued to evaluate the safety and tolerability of the proposed combination.

Part 2: 18 patients will be enrolled in the phase 2 portion of the trial.

**Population:**

Patients with histologically confirmed, potentially curable squamous-cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma of E/GEJ who are candidates for neoadjuvant therapy and surgical resection.

**Investigational drugs:**

Avelumab (Provided by EMD Serono).

IND information to be added as needed.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| 3D-CRT | 3-D conformal radiotherapy |
| ADCC | Antibody-dependent cell-mediated cytotoxicity |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| cc | Cubic centimeter |
| CR | Complete response |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTV | Clinical tumor volume |
| DFS | Disease free survival |
| DLT | Dose Limiting Toxicity |
| DSMC | Data and Safety Monitoring Committee |
| E/GEJ | Esophageal and gastroesophageal junction |
| EC | Esophageal cancer |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | End of treatment |
| FDA | Food and Drug Administration |
| FFPE | Formalin fixed paraffin embedded |
| GC | Gastric cancer |
| GEJ | Gastroesophageal junction |
| GERD | Gastroesophageal reflux disease |
| GI | Gastrointestinal |
| GTV | Gross tumor volume |
| Gy | Gray |
| HPF | High power field |
| HSR | Hypersensitivity reaction |
| ICF | Informed consent form |
| IFN-$\gamma$ | Interferon gamma |

| | |
|---|---|
| IGRT | Image-guided radiotherapy |
| IHC | Immunohistochemistry |
| IL | Intensity modulated radiotherapy |
| IMRT | Interleukin |
| irAE | Immune mediated adverse event |
| ITV | Internal target volume |
| IV | Intravenous |
| Kg | Kilogram |
| LFT | Liver function tests |
| MoAb | Monoclonal antibody |
| NCI | National Cancer Institute |
| OAE | Other significant adverse events |
| pCR | Pathological complete response |
| PET | Positron emission tomography |
| PD-1 | Programmed death 1 |
| PD-L1 | Programmed death ligand 1 |
| PI | Principal investigator |
| PLT | Platelets |
| PRMC | Protocol Review Monitoring Committee |
| PS | Performance status |
| PTV | Planning target volume |
| SAE | Serious adverse event |
| SCC | Squamous cell carcinoma |
| TIL | Tumor-infiltrating lymphocytes |
| TSH | Thyroid stimulating hormone |
| ULN | Upper limit of normal |
| UWCCC | University of Wisconsin Carbone Cancer Center |
| VCAN | Versican |
| VMAT | Volumetric Modulated Arc Therapy |

# EVALUATION SCHEDULE

## Pre-Operative Phase:

| Treatment Days | Screening[a] | 1 (+/- 2 days) | 8 (+/- 2 days) | 15 (+/- 2 days) | 22 (+/- 2 days) | 29 (+/- 2 days) | 43 (+/- 3 days) | 57 (+/- 3 days) | 71 (+/- 7 days) | ~80-100 (+/- 5 days) |
|---|---|---|---|---|---|---|---|---|---|---|
| Carboplatin (AUC2), Paclitaxel (50 mg/m$^2$), IV; weekly | | x | x | x | x | x | | | | |
| Radiation Therapy | | 23 fractions, given M-F; estimated completion day 35 | | | | | | | | |
| Avelumab (10 mg/kg IV), Q14 days | | | | | | x | x | x | | |
| Surgical Resection | | | | | | | | | | x |
| Informed Consent | x | | | | | | | | | |
| Demographics | x | | | | | | | | | |
| Medical History | x | | | | | | | | | |
| Medications | x | x | | x | | x | x | x | x | |
| Physical exam | x | x | | x | | x | x | x | x | |
| Vital Signs[b] | x | x | | x | | x | x | x | x | |
| Lab Tests[c] | x | x | x | x | x | x | x | x | x | |
| Pregnancy Test[d] | x | | | | | | | | | |
| AE's Evaluation | | x | | x | | x | x | x | x | |
| Radiologic Evaluation[e] | x | | | | | | | | x | |
| Plasma for Correlates | | | | | | x | | x | | |
| Serum for Correlates | | | | | | x | | x | | |
| Tissue for Correlates[f] | | x | | | | | | | | x |

[a.] Screening period of 21 days.

[b.] Vital signs should include blood pressure, heart rate, respirations, temperature, height and weight. Height will be measured at screening visit only.

[c.] During the screening period, lab tests will include complete blood count (CBC), absolute neutrophil count (ANC), platelets (PLT), albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, and Hepatitis B/C testing Labs done during the screening period will be used for eligibility determination. On days 1, 8, 15, and 22 lab collection will include CBC, ANC, PLT, bicarbonate, BUN, chloride, creatinine, glucose, potassium, and sodium. On day 29, 43, 57 and 71 lab tests will include the same labs as performed during the screening period. Thyroid stimulating hormone (TSH) and free T4 will be tested on days 29 and 71 only.

[d.] Urine or serum pregnancy test (women of childbearing potential) will be obtained at the time of study enrollment. Urine pregnancy test will also be performed at least once a month while on treatment.

[e.] Baseline PET/CT must be performed within 3 weeks of trial enrollment to ensure subjects have no evidence of metastatic disease and are eligible for participation. While on study, subjects will undergo a restaging PET/CT ~ 1-2 weeks after the last dose of avelumab to evaluate treatment response.

[f.] Archival tissue at baseline. Some of the tissue from surgical resection will be used for correlative studies. See section 9.3

## Post-Operative Phase:

| Treatment Days | 0[a] | 1[b] (+/- 3 days) | 15 (+/- 3 days) | 29 (+/- 3 days) | 43 (+/- 3 days) | 57 (+/- 3 days) | 71 (+/- 3 days) | 30-day Follow-up[f] (+/- 7 days) | Surveillance[g] | Long-Term Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| Avelumab IV (10 mg/kg IV), every 14 days | | x | x | x | x | x | x | | | |
| Medications | x | x | x | x | x | x | x | x | x | |
| Physical Exam | x | x | x | x | x | x | x | x | x | |
| Vital Signs[c] | x | x | x | x | x | x | x | x | x | |
| Lab Tests[d] | | x | x | x | x | x | x | x | | |
| Pregnancy Test[i] | | x | | | | | | | | |
| AE's Evaluation | x | x | x | x | x | x | x | x | x | |
| Radiologic Evaluation[e] | | x | | | | | | x | x | |
| Plasma for Correlates | | x | | | | | x | | x[h] | |
| Serum for Correlates | | x | | | | | x | | x[h] | |
| Survival[g] | | | | | | | | | | x |

[a.] This first post-operative visit should occur 2-4 weeks after surgical resection, unless there are complications that delay this follow-up appointment.

[b.] Avelumab treatment should begin within 12 weeks after the surgical resection. It can begin as early as it is deemed to be safe from the standpoint of surgical recovery in the opinion of the treating physician. Avelumab will be continued for a total of ~ 3 months (i.e. for three 28 day cycles or 6 doses every 14 days) post-operatively.

[c.] Vital signs should include blood pressure, heart rate, respirations, temperature, and weight. Height required at day 0.

[d.] Prior to each post-operative avelumab treatment, labs will include CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium. TSH and free T4 will be checked on day 1 and day 57. Labs during follow-up visit (~ 30 days after adjuvant therapy completion) will include the same labs as on day 1 of adjuvant avelumab treatment initiation.

[e.] A new baseline CT of chest without contrast, and CT abdomen and pelvis with contrast will be obtained within 2 weeks prior to the first dose of adjuvant avelumab administration. The first surveillance scan (CT of chest, abdomen and pelvis) will be obtained within 7 days prior to the visit at 30 days post last dose of adjuvant treatment.

[f.] Follow-up visit will occur ~30 days after last dose of adjuvant treatment. At ~90 days after last dose of avelumab treatment, patients will be contacted via telephone to assess for any delayed immune-related toxicities. If there are any signals of such toxicities, a clinic visit will be scheduled for a more detailed assessment by the study physician.

g. Subjects will be followed with active surveillance while on trial for 12 months after the completion of all planned treatments (calculated from 14 days after last dose of adjuvant treatment). Subjects will have clinic visits approximately every 16 weeks (+/- 14 days) after the first post-treatment radiological evaluation. Surveillance scans (CT of chest, abdomen, and pelvis) will be obtained approximately every 16 weeks, starting after the completion of all adjuvant therapy, during the 12 months of surveillance while on the study. After final surveillance visit at 12 months post adjuvant therapy completion, patients will be followed per discretion of their treating provider. Survival and disease status data will be collected over a time period of up to 3 years from medical records and phone interviews. Labs are not mandatory during surveillance visits, but labs may be obtained as clinically indicated in the opinion of the treating physician.

h. Final correlative blood samples will be drawn at last planned surveillance visit ~ 12 months after adjuvant therapy completion (completion = 14 days after last dose).

i. Urine pregnancy test will be performed prior to start of adjuvant treatment and at least once a month while on treatment.

# 1. BACKGROUND AND RATIONALE

## 1.1 Esophageal Cancer

Esophageal cancer is a major health problem in the world. In Western countries, lower esophagus is the most common site for esophageal cancers, and these tumors frequently involve gastroesophageal junction (GEJ). There are two major histological subtypes of esophageal cancer: squamous carcinoma and adenocarcinoma. Although the incidence of squamous cell esophageal cancer has been declining, esophageal adenocarcinoma has one of the fastest growing incidence among solid tumors in the Western world. Esophageal adenocarcinoma is more common in males, but over the last few decades its rates among women have been increasing as well [1]. Tobacco and alcohol abuse are major risk factors for esophageal SCC, while obesity and gastroesophageal reflux disease (GERD) predispose to the development of esophageal adenocarcinoma. The majority of patients are diagnosed with at least stage II disease, which requires multimodality therapy. Despite aggressive treatments of potentially curative esophageal cancer, about 50% of patients ultimately developed recurrent disease [2]. Further treatment strategies are needed to improve recurrence free survival in this patient population since metastatic esophageal cancer is universally fatal with current treatment options.

## 1.2 Current Treatment Paradigm of Resectable Esophageal Cancer.

Trimodality therapy is the standard approach in the treatment of resectable stage II or higher esophageal cancer. This method is based on the results of a large randomized clinical trial (CROSS) that demonstrated superior survival in patients receiving neoadjuvant chemoradiotherapy followed by surgical resection compared to patients treated with surgery alone 2,3. In this trial, subjects with trimodality arm were treated concurrent chemoradiation that consisted of weekly radiosensitizing carboplatin (AUC 2) and paclitaxel (50 mg/m2) for 5 weeks along with daily radiation for a total dose of 41 Gray (Gy) in 23 fractions 3. This treatment was well tolerated. Over 90% of patients received all scheduled treatments, and there was no increase in postoperative complications. Neoadjuvant therapy resulted in higher rates of R0 resection and lower rates of lymph node involvement in resected specimen compared to the control arm. Pathological complete response was see in 29% of patients (23% for adenocarcinomas and 49% for SCC) 3. Pathological complete response at the time of resection is strongly linked to better survival. CROSS trial demonstrated superior survival in patients

treated with trimodality therapy. However, with current strategies pathological complete response is achieved in a minority of patients. The remaining patients, especially those with positive lymph nodes at the time of the resection, are at significant risk for recurrences. Five-year survival rate for these patients is only 37%, and overall survival is as low as 9 months for those with persistent lymph node disease at the time of resection 4,5. Among patients who develop recurrent disease, most present with distant metastases outside of the radiation field 6. This is not surprising since the accepted treatment paradigm for this disease does not target possible disseminated microscopic disease present at the time of diagnosis. Utilized chemotherapy regimen serves primarily as a radiation sensitizer and has limited activity outside of the radiation field. Prolonged recovery after extensive surgery makes it challenging for many patients to receive additional therapies in post-operative settings. In a similar patient population with resectable gastric cancer treated with peri-operative chemotherapy, less than 50% of patients were able to receive all planned post-operative treatments 7. In May 2021, adjuvant nivolumab was approved in adjuvant setting, This approval was based on the results from randomized phase 3 trial that enrolled patients with resectable esophageal and GEJ cancers treated with preoperative chemoradiation per CROSS and who had residual disease at the time of resection. The benefits were most pronounced in patients with SCC. \These results suggest that novel strategies that involve immunotherapy are warranted to improve outcomes in patients with upper gastrointestinal (UGI) malignancies.

## 1.3 Immunotherapy in the Treatment of Gastroesophageal Cancers

Programmed death ligand 1(PD-L1) is a transmembrane protein that is expressed in about 40% of UGI tumors. PDL1 is one of the ligands for programmed death 1 (PD-1), which is an inhibitory receptor that belongs to the CD28-B7 family. Binding to PD1 results in down regulation of the T cell immune response allowing PDL1 positive tumors to evade immune mediated cell death. PDL1 expression has been shown to be associated with greater depth of muscle invasion, the presence of lymph node metastasis, and overall worse prognosis[8,9]. A number of immunotherapy agents have demonstrated activity against metastatic gastroesophageal cancers. Nivolumab, an antibody that blocks PD1 receptor, is not approved in combination with chemotherapy for patients with untreated advanced gastric, esophageal and GEJ adenocarcinoma based on the results of phase 3 trial Checkmate 649 [11]. Pembrolizumab (another anti PD1 antibody) is approved in combination with chemotherapy in the 1$^{st}$ line treatment of advanced esophageal cancer based on the results of phase 4 Keynote 590 trial. Both of these agents have also demonstrated activity in more advanced setting in biomarker defined patient population [12,13]. Avelumab has been found to have encouraging results in this disease when looking at biomarker defined patient population [14]. Most recently, nivolumab was approved in the adjuvant setting after resection of esophageal and GEJ cancers treated with preoperative chemoradiation and who had residual disease at the time of resection [16].

## 1.4 Avelumab

### 1.4.1 Pharmacology and Pre-Clinical Data

Avelumab is a full human antibody of the immunoglobulin G 1 isotype that specifically targets and blocks programmed death ligand 1 (PD-L1), the ligand for program death 1 (PD-1) receptor. The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell

activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo resulting in the restoration of cytotoxic T cell response. Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The in vitro study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN-γ production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1. In pre-clinical studies, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Radiation therapy in particular was found to be a highly synergistic with avelumab; this treated resulted in complete regression of established tumors probably through generating anti-tumor immune memory.

### 1.4.2 Clinical Experience with Avelumab

There are a number of ongoing Phase 1, 2, and 3 clinical trials evaluating avelumab in the treatment of different malignancies. Avelumab has been studied for its activity in gastric and esophageal cancer. In a Phase 1B trial presented at ASCO 2016 meeting, avelumab was explored for its activity against gastroesophageal cancer. In this early trial avelumab treatment resulted in 15% RR in patients who have progressed on standard chemotherapy [15]. Avelumab is currently being investigated in a randomized trial in similar setting, as well as for its role as maintenance therapy in metastatic disease. The safety for avelumab is based on 1300 subjects treated across different trials. Most of the observed adverse events (AEs) were either in line with those expected in subjects with advanced solid tumors or with class effects of monoclonal antibodies (MoAbs) blocking the PD-1/PD-L1 axis. In addition, infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

## 1.5 Rationale for Adding Avelumab to Neoadjuvant Chemoradiation.

A number of preclinical and clinical studies demonstrated synergism between radiation and immunotherapy, suggesting that combining these approaches can enhance anti-tumor activity and increase treatment efficacy [17-19]. Local radiotherapy is thought to induce an immunostimulatory form of cell death via activation of multiple pro-inflammatory pathways and induction of changes in tumor microenvironment [19]. Although radiation induces chemokines that promote recruitment of effector CD8 cell and T-helper CD4 cells, it has also been shown to induce local upregulation of the PD-L1, which blocks antitumor immunity [18,20,21]. In esophageal cancers, neoadjuvant chemoradiation has been shown to upregulate PDL1 expression by over 50% compared to pre-treatment baseline [22]. In preclinical models, combination of radiation with immune checkpoint inhibitors demonstrated impressive synergism [17,21]. In clinical practice, treatment with ipilimumab or granulocyte–macrophage colony-stimulating factor has been shown to increase the incidence of abscopal events in patients with melanoma [23]. There a number of ongoing clinical trials evaluating synergism between in radiation and immunotherapy in other disease types, including lung cancer,

melanoma, and other solid tumors (clinicatrials.gov). Hence, given the fact that a number of immune checkpoint inhibitors have demonstrated promising activity in a subset of patients with metastatic esophageal and gastric cancers, moving these agents into neoadjuvant setting and combining with chemoradiation may increase the cure rate of this disease [24]. This approach takes advantage of the discussed synergism between immunotherapy and radiation. In addition, immunotherapy treatment will target both local and systemic disease, which is not addressed with the current treatment paradigm.

## 1.6 Benefit/Risk and Ethical Assessment

Based on current clinical experience with immunotherapy in metastatic setting, we hypothesize that adding avelumab to the neoadjuvant therapy can increase cure rate in some patients with this disease. Although increased toxicities may be seen when avelumab is combined with chemoradiation, we anticipate that overall the proposed regimen will be tolerable and will provide additional efficacy for a patient population with significant recurrence rates using current treatment strategies. This clinical trial is designed to avoid compromises to standard neoadjuvant therapy in the studied patient population. In addition, a run-in phase is built in to ensure there is appropriate safety evaluation of the proposed treatment. No new safety signal were seen during evaluation of toxicities after the first 6 patients enrolled in this trial. If this study has promising results, future trials may also explore the use of this approach in larger randomized trials.

# 2. STUDY OBJECTIVES/ENDPOINTS

## 2.1 Part 1

The primary objective of part 1 of the trial is to evaluate the safety of avelumab when combined with chemoradiation in the treatment of resectable E/GEJ cancer.

## 2.2 Part 2

Part 2 will further evaluate the safety and tolerability of the studied drug combination. It will also study activity of avelumab in combination with neoadjuvant chemoradiation in the treatment of resectable E/GEJ cancer.

Primary Endpoint:

- Pathologic complete response (pCR) rate.

Secondary Endpoints:

- Safety and tolerability.
- Disease free survival.
- Incidence of surgical complications.
- Rate of R0 resection.

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall Study Design

The study is a two-part phase 1/2 clinical trial conducted in one center. Part 1 is a run-in phase with the objective to assess the safety and tolerability of avelumab in combination with chemoradiation. Adjuvant avelumab treatment will not be included in DLT evaluation. Part 1 will enroll 6 patients, after which further accrual will be stopped temporarily while safety data is being obtained. The second part of the trial will be an open-label phase 2 study. Part 2 will obtain further safety data of the proposed drug combination and will evaluate the anti-tumor efficacy of perioperative avelumab and chemoradiation in this patient population. Part 2 of the trial will enroll 18 additional patients.

The study will consist of 3 parts: a 21 day screening period, treatment procedures (neoadjuvant therapy, resection and adjuvant therapy), active surveillance for a year after the completion of adjuvant therapy. After the final planned active surveillance visit at 12 months post treatment completion, survival data and disease status will be collected via phone calls or medical record review every 6 months during the following 3 years.

## 3.2 Part 1: Run-In Phase

Six patients will be enrolled in the run-in phase. The goal of this part is to establish safety and tolerability of avelumab when used in combination with chemoradiation. Safety evaluation will last until the first post-operative clinic visit at about 2-4 weeks after resection. Trial enrollment will resume after at least 5 patients do not have a DLT during the DLT evaluation period or until all 6 patients are seen for post-operative evaluation. Subjects during the run-in phase will be allowed to proceed with adjuvant avelumab therapy while DLT evaluations on other subjects are ongoing. If 2 or more patients experience dose-limiting toxicities (DLT) associated with the proposed treatments, further accrual of the subjects will be halted and trial will be suspended. Trial may be reopened in the future with appropriate schedule and dose modifications of the proposed treatment.

### 3.2.1 Definitions of Dose-Limiting Toxicities

For the purposes of this trial DLT will be defined as an adverse event (AE) that occurs after avelumab administration during preoperative period that is clinically significant and/or unacceptable, and is judged to be a related to the avelumab treatment by the investigator. DLT evaluations will occur only during the first part of the trial. Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 will be used in DLT definition.

Definition of DLTs:

- Any complication directly related to neoadjuvant therapy with avelumab that results in the delay in surgical resection, such that resection occurs more than 10 weeks post chemoradiation completion.
- Any complications from neoadjuvant therapy that precludes surgical resection. Disease progression that prevents surgical resection is not considered a DLT. Medical comorbidities that are not related to neoadjuvant therapy in the opinion of the investigator, but which preclude safe surgical resection, are not considered a DLT.

- Any grade 3 immune mediated event (with the exception of esophagitis) that fails to resolve with treatment interruption and systemic steroid administration (if needed) prior to surgical resection.
- Any grade 4 treatment related non-hematologic toxicities excluding alopecia.
- Any avelumab related toxicity that prevents completion of at least 2 of the 3 planned doses in neoadjuvant setting.

## 3.3 Part 2: Expansion Cohort

The second part of the trial will enroll 18 additional patients to evaluate activity of the proposed treatment and to obtain further safety information.

## 3.4 Post-Treatment Surveillance

All patients treated on this study will be followed with active surveillance for 1 year after all planned treatment completion while on protocol. Active surveillance will include clinic visit every 16 weeks and surveillance CT of chest, abdomen and pelvis every 16 weeks during the first year after the treatment completion. Clinic visits and scans can be performed more frequently if clinically indicated. During surveillance visits, labs will be performed only if clinically indicated. Additional procedures, such as endoscopy should be performed as clinically indicated. After the study is completed at 1 year post the completion of adjuvant therapy, active surveillance will be continued per discretion of the treating physician. Surveillance tests after 1 year will not be mandated by the protocol. Survival data and disease status will be collected from either patients or treating physicians every 6 months for up to 3 years after the study completion.

## 3.5 Rationale for Study Design and Doses

The study will use previously established doses of carboplatin and paclitaxel when used in combination with radiation in neoadjuvant setting for the treatment of E/GEJ cancer. This treatment paradigm was established based on the on randomized phase III trial evaluating this approach [3]. Avelumab will be administered at its standard dose of 10 mg/kg IV every 2 weeks. During pre-operative period, three doses of avelumab will be administered starting on day 29 of treatment. It will be started on the same day as the last (fifth) chemotherapy infusion. The schedule of avelumab administration was chosen to optimize the synergism between chemoradiation and immunotherapy, but also to avoid any compromise to the standard of care chemoradiation administered to this patient population. A total of 3 months (6 treatments every 2 weeks) of adjuvant avelumab will be administered post-operatively. Additional avelumab treatments were built into the protocol to maximize potential benefits of avelumab on systemic recurrences. Three months duration was chosen to mimic perioperative gastric cancer treatment standards, where 9 weeks of preoperative and 9 weeks post-operative chemotherapy is typically recommended based on MAGIC trial [7]. Similar to this approach, with the proposed treatment schema patients will receive a total of 18 weeks of avelumab.

# 4. PATIENT SELECTION CRITERIA

## 4.1 Study Population

This study will enroll patients with stage II/III E/GEJ cancer who are candidates for neoadjuvant therapy and surgical resection with curative intent.

## 4.2 Inclusion Criteria

1. Patients with histologically confirmed, potentially curable squamous-cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma of the esophagus and GEJ (Siewert type 1-3).
2. Locoregional disease with clinical stage of T1N1 or T2-3N0-2.
3. No clinical evidence of metastatic spread. Staging should include endoscopic ultrasound and PET/CT as recommended by NCCN guidelines. PET/CT should be performed within 3 weeks of signing informed consent.
4. Age 18 years or older.
5. ECOG performance status 0-2.
6. Subjects must be deemed to be potential surgical candidates by an evaluating surgeon.
7. Adequate organ function:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Hemoglobin $\geq 9$ g/dL (transfusions allowed)
    c. Platelets $\geq 100 \times 10^9$/L
    d. AST/ALT $\leq$ 2.5 x ULN
    e. Total serum bilirubin of $\leq$1.5 x institutional upper limit of normal (ULN)
    f. Estimated creatinine clearance $\geq 30$ mL/min according to the Cockcroft-Gault formula
8. Female patients of childbearing potential must have a negative pregnancy test (urine or serum) within 21 days prior to the start of the study drug treatment and must agree to use adequate birth control if conception is possible during the study and up to 30 days after the completion of adjuvant therapy.
9. Male patients must agree to use adequate birth control during the study and up to 30 days after the last avelumab dose.
10. Women who are nursing must discontinue breast-feeding prior to the enrollment in the trial.
11. Patient must be able and willing to comply with study procedures as per protocol.
12. Patient able to understand and willing to sign and date the written voluntary informed consent form (ICF) at screening visit prior to any protocol-specific procedures.

## 4.3 Exclusion Criteria

1. Prior history of radiation to the mediastinum.
2. Diagnosis of cervical esophageal carcinoma.
3. Other active malignancy within the last 3 years (except for non-melanoma skin cancer, a non-invasive/in situ cancer, or indolent non metastatic Gleason 6 prostate cancer).
4. Subjects with an active or known autoimmune disease. Subjects with type I diabetes mellitus, hypo- or hyperthyroidism only requiring hormone replacement/suppression, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic immunosuppressive treatment are eligible.
5. Current use of immunosuppressive medication, except for the following:
    a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)
    b. systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
6. Active infection requiring systemic therapy at the time of study treatment initiation.
7. Prior organ transplantation including allogenic stem-cell transplantation.
8. Known history of testing positive for HIV or known immunodeficiency syndrome
9. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
10. Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines..
11. Major surgery within prior 4 weeks of treatment initiation (the surgical incision should be fully healed prior to all neoadjuvant treatment initiation).
12. Any prior anticancer therapy for esophageal cancer.
13. History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin, paclitaxel or avelumab, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade ≥ 3).
14. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication. Patients with stable rate-controlled atrial fibrillation will be allowed to participate.

15. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study

16. Psychological, familial, or sociological condition potentially hampering compliance with the study protocol and follow-up schedule.

## 4.4 Replacement Criteria

- In Part 1 of the study, patients who discontinue the study due to a DLT will not be replaced.
- Patients who discontinue the study prior to receiving any avelumab doses will be replaced in parts 1 and 2 of the study.
- Patients who are not taken to surgery because of issues unrelated to neoadjuvant therapy (such as undiagnosed prior comorbidities, patient preference) will be replaced in parts 1 and 2.
- Patients who develop progressive disease after avelumab has been started will not be replaced.

# 5. TREATMENTS

All patients will receive weekly carboplatin and paclitaxel while undergoing radiation therapy. Chemotherapy will be started on day 1 of radiation and will be given every 7 days. A total of 5 planned weekly chemotherapy treatments will be administered during the course of the study. Radiation will be administered Monday – Friday until the planned course is completed. Avelumab will be given every two weeks starting on the same day as the last chemotherapy infusion (day 29). If the last dose of chemotherapy is omitted due to cytopenias, avelumab will still be administered as originally planned. Avelumab will be continued after radiation is completed. A total of 3 doses of avelumab will be administered during the preoperative period. Additional 6 doses of avelumab will be administered post-operatively.

## 5.1 Chemotherapy Administration

Paclitaxel 50 mg/m$^2$ and Carboplatin (AUC 2) will be given via intravenous infusion on days 1, 8, 15, 22 and 29. Standard of care procedures and institutional guidelines will be followed during the administration of these agents. Detailed information about carboplatin and paclitaxel can be obtained from drug package inserts.

Patients who start treatment with paclitaxel are at risk for hypersensitivity reaction (HSR). All patients should be premedicated prior to paclitaxel administration in order to prevent severe HSRs. Premedication regimen will consist of dexamethasone 12 and 6 hours before treatment,

diphenhydramine (or its equivalent) 50 mg IV 30 minutes prior to chemotherapy, and ranitidine 50 mg IV 30 minutes prior to chemotherapy. Oral dexamethasone doses will be 20 mg before day 1 treatment, 12 mg before day 8 treatment, and 8 mg before day 15 treatment. Patients who do not take dexamethasone at home will receive IV dexamethasone before paclitaxel infusion: 20 mg IV prior to day 1 treatment and 8 mg IV before day 8 and day 15 of treatment. Patients who do not experience hypersensitivity reaction during the first 3 paclitaxel infusions with the above premedication regimen will be asked to stop further premedication with dexamethasone during subsequent treatments since their risk for subsequent significant HSR is very low [25]. This change in premedication is done to prevent any potential counteractivity of the steroids with immunotherapy. These patients will continue to receive diphenhydramine and ranitidine. Dexamethasone can be reinstituted as needed if HSR were to develop. Subjects can continue with the study protocol even if dexamethasone is required for premedication prior to chemotherapy infusion.

## 5.2 Avelumab Administration

### 5.2.1 Dosing and Administration of Avelumab

Avelumab 10mg/kg will be administered intravenously every 2 weeks for 3 doses prior to surgery and for 6 doses as adjuvant treatment postoperatively. Avelumab dose will be adjusted accordingly if subject's weight changes more than 10% compared to prior treatment or baseline. A new baseline weight will be obtained prior to the first post-operative avelumab dose administration. In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine (IV or oral) and 500-650 mg acetaminophen. Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.

Avelumab will be diluted in Sodium Chloride 0.9% 250mL and infused IV over 60 minutes (-10/+20 minutes) via a 0.2 micron in line filter. Immediately following the infusion of avelumab, it is recommended (but not mandatory) to conduct a normal saline flush using the same tubing and 25-100 mL normal saline infused at the same rate to clear the infusion set of residual drug.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), antihistamines, bronchodilators, or equivalents, and oxygen should be available for immediate access along with equipment for assisted ventilation. Following the avelumab infusion, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

### 5.2.2 Packaging, Labeling, Storing and Preparation

Avelumab is provided by EMD Serono in a form of a sterile, clear, colorless and non-pyrogenic solution for intravenous infusion. It will be presented in Type I glass vials filled with 10 mL of liquid (200 mg/vial), closed with a rubber septum and sealed with an aluminum flip off seal.

Each single-use vial contains 200 mg of avelumab, formulated as a 20 mg/mL preservative-free acetate buffered solution at pH 5.2 in presence of Polysorbate 20 and Mannitol. This product will require further dilution prior to IV infusion. Vials must be stored under refrigeration at (2ºC-8ºC) in an environment with temperature control devices. Temperatures must be recorded on a daily basis. Vials must not be stored at room temperature, frozen or shaken vigorously. Vials must be warmed up to room temperature by removal from the refrigerator for 30 (+20) minutes before preparing each dose. Avelumab infusion solution should be prepared by dilution in 0.9% Sodium Chloride (Normal Saline) (or in 0.45% Sodium Chloride, only if the first option is not applicable). The verified avelumab concentration range in the infusion solution is 0.016 mg/mL to 8 mg/mL. Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and institutional procedures.

### 5.2.3 Avelumab Product Accountability

Avelumab must not be used for any purpose other than this clinical trial. The administration of trial drug to subjects who have not been enrolled is considered a protocol deviation.

Rigorous drug accountability will be maintained at all times and will include (at minimum) the following information: record of product receipt, perpetual inventory (including batch/lot number and quantity), subject dosing and utilization, and disposal. All clinical study drug provided by EMD Serono will be fully reconciled and any unused vials will be either returned to the EMD Serono or destroyed after trial completion with required documentation.

## 5.3 Radiation Therapy

The radiation will be administered concurrently with the chemotherapy. Both 3-D conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) will be allowed. The IMRT may be delivered with either conventional IMRT, Volumetric Modulated Arc Therapy (VMAT) or helical IMRT (tomotherapy).

### 5.3.1 Dose Specification

The planned total dose will be 41.4 Gray (Gy) in 23 fractions at 1.80 Gy/day. Patients will be treated 5 days/week; patients will receive the 41.4 Gy over an approximately 4-1/2-week period. The daily prescription dose will be to the selected isodose curve, 95% of which must encompass the entire planning target volume (PTV).

### 5.3.2 Volume Definitions

Gross tumor volume (GTV) will include all FDG avid regions by PET/CT or areas of involvement identified by EUS or CT (whichever is larger). Clinical tumor volume (CTV) consists of a minimum of 4 cm proximal and distal and 1 cm lateral beyond the GTV of the primary tumor. In addition, involved regional lymph nodes will have a ≥ 1 cm CTV in all dimensions, and the involved nodal region can be included at the physician's discretion. CTVs may be edited off of uninvolved normal tissues.

PTV will provide a margin around the CTV to compensate for variability in treatment setup, breathing, or motion during treatment. A margin around the CTV will define the PTV. The PTV volume must include a minimum of 0.3 cm and a maximum of 2 cm around the CTV. Margins can be adjusted as necessary to avoid excessive normal organ exposure, as defined in section 5.2.5. Use of cross-sectional imaging based image-guided radiotherapy (IGRT) may further limit PTV volume.

### 5.3.3 Treatment Planning

A PET and CT scan (preferably a PET/CT) for diagnosis and volumetric treatment planning is required. Planning and treatment will be performed with the patient in supine position with body immobilization. Treatment will be given free breathing or at breath hold with gating per the treating physician's discretion. Three mm or smaller CT slices will be obtained from the thoracic inlet to the mid-abdomen as part of the PET/CT. A 4D CT simulation may be obtained to evaluate internal target motion and create an internal target volume (ITV) for better definition of PTV margins. All plans will be limited to the dose constraints as described below.

The spinal cord, liver, lung, and heart will be contoured in their entirety. The lungs, heart, spinal cord, and liver will be the considered the primary dose-limiting structures. When planning the beam arrangement to the PTV, the lungs, heart, spinal cord, and liver should be out of the field to the greatest extent possible. The dose per fraction to the lungs, heart, and spinal cord should be maintained at 2 Gy or less per fraction to the greatest extent possible. If tolerance dose to any of the normal organs is exceeded in a treatment plan, alternate beam arrangements should be used.

Maximum dose to the PTV should not exceed the prescription dose by >10 %. The maximum point dose to critical normal structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

#### *5.3.3.1 Critical structures*

- Spinal cord dose will be limited to < 0.1 cc of the cord receiving ≥ 40.0 Gy.
- Heart: Heart mean dose of < 25 Gy.
- Liver: mean liver dose not to exceed 25 Gy.
- Lung: the volume(V) of lung outside of the PTV that receives 20 Gy will be limited to < 30% (V 20 < 30%). Mean lung dose < 18 Gy.
- Kidney: combined kidneys V 20<33%, each individual kidney V 20<50%.

### 5.3.4 Quality Control

Dose heterogeneity: Maximum dose to PTV should not exceed the prescription dose by > 10%. The maximum point dose to critical normal structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

### 5.3.5 Treatment Verification

First day portal, CT or MRI images of each field must be obtained for position verification. At least once weekly verification films or images will be obtained per institutional guidelines. For IMRT or PTV margins of less than 5mm, daily 3D imaging is required.

### 5.3.6 External Beam Equipment

Mega-voltage radiation therapy will be used. IMRT treatment planning and delivery, including with tomotherapy, can be used in lieu of 3D conformal planning as described above.

## 5.4 Surgical Resection

Surgical resection will be performed ~8 weeks after the completion of chemoradiation. The most appropriate surgical intervention will be chosen by the operating surgeon. Resected specimen will be evaluated in our pathology department for any residual disease and treatment effect. Part of the resected specimen will also be evaluated in Dr. Deming's research laboratory for correlative biomarkers.

## 5.5 Concomitant and post-study treatment(s)

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient from ≤ 7 days prior to the first day of neoadjuvant treatment initiation to the end of treatment visit. All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, will be recorded during the screening and treatment period, starting from the date of signature of informed consent, and ending at follow up visit. Vaccination with live vaccines within 4 weeks of the first dose of avelumab and while on trial is prohibited.

## 5.6 Restrictions During the Study

### 5.6.1 Administration of Other Anti-Cancer Agents

Administration of anti-cancer agents other than those specified in the protocol is not allowed during study enrolment.

### 5.6.2 Immunosuppressive Agents

The use of immunosuppressive agents is prohibited during the treatment with avelumab and until surgical resection, including immunosuppressive doses of systemic corticosteroids. Subjects will be allowed to use topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted at doses of ≤ 10 mg of daily prednisone (or equivalent). A brief course of corticosteroids for prophylaxis (e.g., for contrast dye allergy or to prevent taxane related hypersensitivity reaction) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. However, it is preferable that steroid premedication is reduced or omitted by week 22 of treatment if no hypersensitivity reaction with taxanes has been observed during prior weeks.

### 5.6.3 Pregnancy and Contraception

All patients must be made fully aware of the information relating to the potential for reproductive toxicity as detailed in the Informed Consent Form. Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 30 days after the completion of the adjuvant therapy.

Women of childbearing potential

Females of childbearing potential should use reliable methods of contraception from the time of screening until 30 days post the completion of adjuvant therapy. Acceptable methods of contraception include tubal ligation, oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g,. Depo-Provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

Males

Male patients must use a condom during sexual intercourse with female sexual partners including a pregnant partner during the study and for 30 days after the completion of adjuvant therapy. Male patients should avoid procreation during the trial and for 30 days after the completion of adjuvant therapy.

# 6. STUDY PROCEDURES.

Patients who are eligible for the study will be enrolled in the clinical trial after they provide informed consent for study participation. There will be no randomization in this trial. This is an open label trial.

## 6.1 Visit Schedule and Assessments

**Screening Visit (within 21 days of treatment initiation):**

- Review eligibility criteria
- Demographic data
- Review cancer history
- Review past medical history and surgical history
- Vital Signs (weight, height, blood pressure, heart rate, temperature)
- ECOG performance status determination (Appendix B)
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Medication reconciliation
- Lab work: CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium, Hepatitis B/C testing
- Obtain informed consent for trial enrollment

**Days 1, 8, 15, 22 (+/- 2 days):**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation (day 1 and 15 only)
- ECOG performance status determination (day 1 and 15 only)
- Complete physical examination (on days 1 and 15 only); complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions (day 1 and 15 only)
- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work: CBC, ANC, PLT, bicarbonate, BUN, chloride, creatinine, glucose, potassium, and sodium
- Carboplatin and paclitaxel administration
- Radiation will be continued daily, Monday – Friday (excluding weekends and holidays) to complete a planned course
- Urine pregnancy test in females of childbearing potential should be performed prior to all treatment initiation and at least monthly during the duration of active perioperative treatment while on the study. Urine pregnancy test will not be performed on monthly basis after all the adjuvant treatment is completed. Urine pregnancy test will not be repeated during hospitalization for surgical resection.

**Day 29 (+/- 2 days):**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions
- Review adverse events that have occurred since the previous visit (starting with cycle 2)
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work: CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium, TSH, free T4
- Carboplatin and paclitaxel administration
- Avelumab administration, after chemotherapy administration is complete. Premedication will be repeated prior to the avelumab administration.
- Radiation will be continued daily, Monday – Friday (excluding weekends and holidays) to complete a planned course
- Blood draw for correlative studies

**Day 43, 57 (+/- 3 days):**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions
- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work: CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium.
- Avelumab administration
- Blood draw for correlative studies (Day 57 only)

**Day 71 (+/- 7 days):**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions
- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work: CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium,TSH and free T4.
- Restaging PET/CT should be performed prior to this visit

**Day 80-100 (+/- 5 days):**

- Surgical resection
- Tumor sample collected for correlative studies

**Post-Operative Follow-up (2-4 weeks after the surgical resection):**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions

- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit

**Adjuvant Avelumab every 2 weeks for a total of 6 doses (i.e. three 28 day cycles), starting within 12 weeks after surgical resection:**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions
- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work: CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium. TSH and free T4 will be obtained on day 1 and day 57 of treatment.
- New baseline CT of chest, abdomen and pelvis must be obtained within two weeks prior to the first dose of adjuvant avelumab administration.
- Blood draws for correlative studies on first and last days of avelumab administration, pre infusion.

**Follow-up Visit, 30 days (+/- 7 days) after adjuvant treatment completion:**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions
- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit
- Lab work: CBC, ANC, PLT, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium, TSH and free T4.
- CT of chest, abdomen and pelvis will be obtained prior to this visit.
- ~90 days after avelumab treatment completion, patients will be contacted via telephone to assess for any delayed immune-related toxicities. If there are any signals of such toxicities, a clinic visit will be scheduled for a more detailed assessment.

**Surveillance Follow Up (every 16 weeks +/- 14 days) after adjuvant therapy completion for a duration of 12 months:**

- Vital Signs (weight, blood pressure, heart rate, temperature)
- Medication reconciliation
- ECOG performance status determination
- Complete physical examination; complete neurological exam is not required unless clinically indicated
- Review occurrence or change of existing conditions
- Review adverse events
- Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
- Surveillance CT chest, abdomen and pelvis should be obtained prior to follow-up visits, approximately every 4 months during the first year adjuvant therapy completion.
- Labs are not required, but can be obtained as clinically indicated in the opinion of the treating physician.

**Survival Follow-Up:**

- Subjects will be followed for survival and disease progression after completing the final surveillance visit. Survival follow up should continue at least every 6 months for 3 years after final surveillance visit or death, whichever is sooner. When possible, the following information will be obtained from subjects (via telephone is acceptable) or medical record (if available):
    - Disease status and date of disease progression or recurrence (if known and applicable)
    - Anti-cancer therapy received since end of treatment visit
    - Date of death (if applicable)

## 6.2 Radiological Evaluations

Subjects will be required to have a restaging PET/CT about 2 weeks after the last avelumab dose to evaluate treatment response and to rule out progressive metastatic disease. After surgical resection, subjects will undergo surveillance CT of chest, abdomen and pelvis every 16 weeks during the first 12 months. There is no requirement for disease assessment after the end of treatment visit. Subjects who stop study treatment before completion for any reason will not be required to follow study imaging requirements.

## 6.3 Procedures for Handling Subjects Incorrectly Enrolled or Initiated On Investigational Product.

Subjects who are incorrectly enrolled in the study will be withdrawn from study participation and replaced. If study treatments have been initiated, patients will be monitored for development of any toxicities.

# 7. TOXICITY MANAGEMENT

## 7.1 General Toxicity Management Guidelines

These guidelines are applicable for toxicity management during the study duration with the exception of the DLT evaluation period in part 1. Any toxicity observed during the course of the study should be managed by interruption and/ or dose reduction of the drug if deemed appropriate by the Investigator. In general, any Grade 4 AE will require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

## 7.2 Hematologic Toxicity

During the pre-operative phase, if on days 8, 15, 22, 29 ANC is < 1000 and PLT < 50, chemotherapy should not be administered and delayed by one week. On day 29, which is the last treatment, chemotherapy can be administered if ANC is ≥ 750. Since bone marrow toxicity is not specifically associated with avelumab, avelumab can be administered even with the above labs. However, avelumab should be held for grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, grade 4 neutropenia or any febrile neutropenia. The first dose of avelumab can be delayed up to 10 days if needed. If the last dose of chemotherapy is not given because of hematologic toxicity and avelumab needs to be delayed, avelumab can be started as soon as there is adequate bone marrow recovery.

## 7.3 Non-Hematologic Toxicity During Chemoradiation

Any Grade ≥ 3 non-hematological treatment related toxicity (except for alopecia or esophagitis) during chemoradiation should result in dose delays of chemotherapy and appropriate supportive measures should be instituted until toxicity resolves to Grade ≤ 2. Radiation should continue as planned unless toxicities are thought to be specifically radiation related and would not resolve without radiation interruption in the opinion of the investigator.

Intravenous therapy and radiation can continue with ongoing grade 3 esophagitis, which can be seen in the setting of esophageal chemoradiation. Appropriate supportive measures should be initiated per institutional practice standards. In some instances, medical support with intravenous hydration and parenteral nutrition may be necessary for support in order to complete the planned neoadjuvant treatment. In the event of grade 4 treatment induced esophagitis all of the treatment should be held until esophagitis resolves to grade ≤ 3.

If radiation has to be interrupted for toxicity, additional radiation days may be added at the end of the treatment. Chemotherapy will be added as needed to match weekly radiation schedule. Avelumab may potentially be started after day 29, but its start date must coincide with the last chemotherapy infusion or be given on the day chemotherapy was planned (if chemotherapy was held for hematologic toxicities as detailed above).

## 7.4 Immune-Mediated Toxicities of Avelumab

Avelumab treatment may result in toxicities related to the activation of immune system and its off-target effects. These immune-related AEs (irAEs) may be seen after the first dose or as late as weeks after the last dose of avelumab.

Dose reduction of avelumab is not allowed. Dose delays or treatment discontinuation may be necessary depending on the grade and timing of the AE. If AEs require more than 2 week delay for the scheduled dose, then avelumab treatment must be discontinued. This does not apply to the first dose of avelumab in neoadjuvant setting, which may be delayed to match the last dose of chemotherapy.

**Any Grade 3 avelumab attributed AEs require treatment discontinuation with avelumab except for any of the following**:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1.
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management. Asymptomatic elevation of amylase or lipase do not require drug interruption or discontinuation, even if these lab abnormalities are thought to be related to avelumab.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given if the ECOG PS is ≥ 3 on the day of study drug administration).
- Grade 3 esophagitis during neoadjuvant therapy does not necessitate treatment discontinuation.

**Any Grade 2 avelumab attributed AEs should be managed as follows:**

- If a Grade 2 AE resolves to Grade ≤ 1 by the next scheduled avelumab administration, treatment may continue.
- If a Grade 2 AE does not resolve to Grade ≤ 1 by the next scheduled avelumab administration, infusions should not be given. If treatment is delayed by more than 2 weeks, the subject should permanently discontinue treatment with avelumab (except for hormone insufficiencies that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted). This is not applicable to esophagitis during neoadjuvant phase of the treatment.

- Upon the second occurrence of the same Grade 2 AE (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued. This is not applicable to esophagitis during neoadjuvant phase of the treatment.
- No treatment interruptions/discontinuation is needed for asymptomatic elevation of amylase or lipase.

For any additional immune mediated toxicities that are not listed in Table 1 below, treatment should be held for any AE of Grade 2 or higher until resolution down to grade 1 or 0. Treatment should be discontinued permanently if toxicities remain at grade 2 or above for over 2 weeks despite supportive measures (including steroids if needed).

**Table 1**: Management of Immune-Related Adverse Events.

| **GASTROINTESTINAL irAEs** | | |
|---|---|---|
| **Severity of Diarrhea / Colitis (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Diarrhea: increase of < 4 stools/day over baseline<br>Colitis: asymptomatic | Continue avelumab therapy<br>Symptomatic treatment (for example, loperamide) | Close monitoring for worsening symptoms<br>Educate subject to report worsening immediately<br>If worsens:<br>Treat as Grade 2, 3 or 4 |
| **Grade 2**<br>Diarrhea: increase of 4 to 6 stools per day over baseline; IV fluids indicated < 24 hours; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | Delay avelumab therapy<br>Symptomatic treatment | If improves to Grade $\leq$ 1: Resume avelumab therapy<br>If persists > 5 to 7 days or recurs: Treat as Grade 3 to 4 |
| **Grade 3 to 4**<br>Diarrhea (Grade 3): increase of $\geq$ 7 stools per day over baseline; hospitalization indicated; limiting self care ADL<br>Colitis (Grade 3): severe abdominal pain, peritoneal signs.<br>Grade 4: life-threatening, urgent intervention indicated | Withhold avelumab for Grade 3.<br>Permanently discontinue avelumab therapy for Grade 4 or recurrent Grade 3.<br>1 to 2 mg/kg/day prednisolone IV or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider lower endoscopy | If improves:<br>Continue steroids until Grade $\leq$ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).<br>If worsens, persists > 3 to 5 days, or recurs after improvement:<br>Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis |

| DERMATOLOGICAL irAEs | | |
|---|---|---|
| **Grade of Rash (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1 to 2**<br>Covering ≤ 30% body surface area | Continue avelumab therapy<br>Symptomatic therapy (for example, antihistamines, topical steroids) | If persists > 1 to 2 weeks or recurs:<br>Withhold avelumab therapy<br>Consider skin biopsy<br><br>Consider 0.5 to 1 mg/kg/day prednisolone or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper.<br>If worsens: Treat as Grade 3 to 4 |
| **Grade 3 to 4**<br>Covering > 30% body surface area; life threatening consequences | Withhold avelumab for Grade 3.<br>Permanently discontinue for Grade 4 or recurrent Grade 3.<br>Consider skin biopsy<br>Dermatology consult<br>1 to 2 mg/kg/day prednisolone or equivalent<br>Add prophylactic antibiotics for opportunistic infections | If improves to ≤ Grade 1:<br>Taper steroids over at least 1 month , resume avelumab therapy following steroids taper (for initial Grade 3) |

| PULMONARY irAEs | | |
|---|---|---|
| **Grade of Pneumonitis (NCI-CTCAE v5)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Asymptomatic; clinical or diagnostic observations only, intervention not indicated | Consider withholding avelumab therapy<br>Monitor for symptoms every 2 to 3 days<br>Consider Pulmonary and Infectious Disease consults | Re-assess at least every 3 weeks<br>If worsens: Treat as Grade 2 or Grade 3 to 4 |
| **Grade 2**<br>Symptomatic; medical intervention indicated; limiting instrumental ADL | Withhold avelumab therapy<br>Pulmonary and Infectious Disease consults<br>Monitor symptoms daily, consider hospitalization<br>1 mg/kg/day prednisolone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | Re-assess every 1 to 3 days<br>If improves:<br>When symptoms return to Grade $\leq$ 1, taper steroids over at least 1 month<br>If not improving after 2 weeks or worsening:<br>or worsening:<br>Treat as Grade 3 to 4 |
| **Grade 3 to 4**<br>Severe symptoms; limiting self care ADL; oxygen indicated ; life-threatening respiratory compromise– urgent intervention indicated(e.g., tracheotomy or intubation) | Permanently discontinue avelumab therapy<br>Hospitalize<br>Pulmonary and Infectious Disease consults<br>1.0 to 2.0 mg/kg/day prednisolone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | If improves to Grade $\leq$ 1:<br>Taper steroids over at least 6 weeks<br>If not improving after 48 hours or worsening:<br>Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) |

| HEPATIC irAEs | | |
|---|---|---|
| **Grade of Liver Test Elevation (NCI-CTCAE v5)** | **Initial Management** | **Follow-up** |
| **Grade 1**<br>AST or ALT > ULN to 3 x ULN; >1.5 to 3.0x baseline if baseline was abnormal and / or total bilirubin > ULN to 1.5 x ULN; >1.0 to 1.5x baseline if baseline was abnormal | Continue avelumab therapy | Continue liver function monitoring<br>If worsens: Treat as Grade 2 or 3 to 4 |
| **Grade 2**<br>AST or ALT > 3.0 to ≤ 5 x ULN; >3.0 to 5.0x baseline if baseline was abnormal and / or total bilirubin > 1.5 to ≤ 3 x ULN ; >1.5 to 3.0x baseline if baseline was abnormal | Delay avelumab therapy<br>Increase frequency of monitoring to every 3 days | If returns to baseline: resume routine monitoring, resume avelumab therapy<br>If elevations persist > 5 to 7 days or worsen:<br>0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy |
| **Grade 3 to 4**<br>AST or ALT > 5 x ULN; >5.0x baseline if baseline was abnormal and / or total bilirubin > 3 x ULN; >3.0x baseline if baseline was abnormal | Permanently discontinue avelumab therapy<br>Increase frequency of monitoring to every 1 to 2 days<br>1 to 2 mg/kg/day prednisolone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consult gastroenterologist/hepatologist<br>Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted | If returns to Grade < 1:<br>Taper steroids over at least 1 month<br>If does not improve in > 3 to 5 days, worsens or rebounds:<br>Add mycophenolate mofetil 1 gram (g) twice daily<br>If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines |

| Renal irAEs | | |
|---|---|---|
| **Grade of Creatinine Increased (NCI-CTCAE v5)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Creatinine increased > ULN to 1.5 x ULN | Continue avelumab therapy | Continue renal function monitoring<br>If worsens:<br>Treat as Grade 2 to 3 or 4 |
| **Grade 2 to 3**<br>Creatinine increased > 1.5 and ≤ 6 x ULN | Withhold avelumab therapy<br>Increase frequency of monitoring to every 3 days<br>1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections<br>Consider renal biopsy<br>Nephrology consult | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper.<br>If worsens:<br>Treat as Grade 4 |
| **Grade 4**<br>Creatinine increased > 6 x ULN | Permanently discontinue avelumab therapy<br>Monitor creatinine daily<br>1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections<br>Consider renal biopsy | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month |

| CARDIAC irAEs | | |
|---|---|---|
| **Myocarditis** | **Initial Management** | **Follow-up Management** |
| New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis. | Withhold avelumab therapy<br><br>Hospitalize.<br><br>In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management<br>Cardiology consult to establish etiology and rule-out immune-mediated myocarditis.<br><br>Guideline based supportive treatment as per cardiology consult.*<br><br>Consider myocardial biopsy if recommended per cardiology consult. | If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy.<br><br>If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. |
| Immune-mediated myocarditis | Permanently discontinue avelumab.<br><br>Guideline based supportive treatment as appropriate as per cardiology consult.*<br><br>Prednisolone 1 to 2 mg/kg/day or equivalent.<br><br>Add prophylactic antibiotics for opportunistic infections. | Once improving, taper steroids over at least 1 month.<br><br>If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A) |
| *Local guidelines, or e.g. ESC or AHA guidelines<br>ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines<br>AHA guidelines website:<br>http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001 | | |

| ENDOCRINE irAEs | | |
|---|---|---|
| **Endocrine Disorder** | **Initial Management** | **Follow-up Management** |
| Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus) | Continue avelumab therapy<br>Endocrinology consult if needed<br>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate.<br>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) | Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |
| **Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)** | Withhold avelumab therapy<br>Consider hospitalization<br>Endocrinology consult<br><br>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate.<br><br>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) | Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).<br><br>Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |
| **Hypopituitarism/Hypophysitis (secondary endocrinopathies)** | If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : | Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).<br><br>In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. |

| | | |
|---|---|---|
| | • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)<br>• Hormone replacement/suppressive therapy as appropriate<br>• Perform pituitary MRI and visual field examination as indicated<br><br>**If hypophysitis confirmed:**<br>• Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month<br>• Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.<br>• Add prophylactic antibiotics for opportunistic infections. | Continue hormone replacement/suppression therapy as appropriate. |

| Other irAEs (not described above) | | |
|---|---|---|
| **Grade of other irAEs (NCI-CTCAE v5)** | **Initial Management** | **Follow-up Management** |
| **Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE** | Withhold avelumab therapy pending clinical investigation | If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy<br>If irAE is confirmed, treat as Grade 2 or 3 irAE. |
| **Grade 2 irAE or first occurrence of Grade 3 irAE** | Withhold avelumab therapy<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month and resume avelumab therapy following steroids taper. |
| **Recurrence of same Grade 3 irAEs** | Permanently discontinue avelumab therapy<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month. |
| **Grade 4** | Permanently discontinue avelumab therapy<br>1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult. | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month |
| **Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency**<br><br>**Persistent Grade 2 or 3 irAE lasting 12 weeks or longer** | Permanently discontinue avelumab therapy<br>Specialty consult | |

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

## 7.5 Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

| NCI-CTCAE Grade | Treatment Modification for Avelumab |
|---|---|
| **Grade 1 – mild**<br>Mild transient reaction; infusion interruption not indicated; intervention not indicated. | • Decrease the study drug infusion rate by 50% and monitor closely for any worsening. |
| **Grade 2 – moderate**<br>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h. | • Temporarily discontinue drug infusion.<br>• Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening. |
| **Grade 3 or Grade 4 – severe or life-threatening**<br>Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.<br>Grade 4: Life-threatening consequences; urgent intervention indicated. | • Stop the avelumab infusion immediately and disconnect infusion tubing from the subject.<br>• Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment. |
| - If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.- If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. | |

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs

## 7.6 Indications for Treatment Discontinuation

Patient must be removed from the study protocol for one of the following reasons:

- Development of metastatic disease.
- Development of locoregional recurrence after the resection.
- Development of locally advanced disease while on neoadjuvant treatment that precludes adequate and safe surgical resection.
- Intercurrent illness that prevents further administration of treatment or surgical resection.
- Unacceptable adverse event(s).
- Severe non-compliance to study protocol as judged by the investigator.
- Patient becomes pregnant.

- Patient is determined to be incorrectly enrolled (i.e., the patient does not meet the required inclusion/exclusion criteria for the study).
- Patient decides to withdraw from the study (the subject is at any time free to discontinue treatment, without prejudice to further treatment).

## 7.7 Procedures for Discontinuation of a Subject From Investigational Product

All reasons for discontinuation of treatment must be documented clearly. Any patient discontinuing investigational therapy should be seen at 30 days post treatment discontinuation for the evaluations, as outlined in the study schedule, or before new treatment initiation (whichever comes first). The patient's tumor status should be assessed clinically and, if appropriate, disease recurrence or progression should be confirmed by radiological assessment. After discontinuation of the study medications, all ongoing or new AEs or SAEs must be followed until resolution unless, in the investigator's opinion, the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up, or a new treatment has been started.

## 7.8 Withdrawal From Study

Subjects who withdraw from the study before treatment initiation will be replaced by other eligible patients. In part 1 of the study, patients who withdraw from the study before any avelumab administration will be replaced.

# 8. STUDY EFFICACY ASSESSMENTS

## 8.1 Pathology Evaluation

Assessment of the histopathologic response to the treatment will be performed by the pathologist. Esophagogastrectomy specimens will be processed according to standard operating procedures within the UWHC Department of Pathology.

### 8.1.1 Pathologic Complete Response

The pathologist will review the slides from the tissue sections submitted in order to assess pathologic compete response (pCR). pCR is defined as an absence of any viable tumor at microscopic examination of the primary tumor and any lymph nodes sampled after surgery following neoadjuvant therapy. Participants with invalid/missing pCR assessments will be defined as non-responders. In patients not achieving pCR, measurement of residual disease will be performed.

### 8.1.2 Assessment of Treatment Effect

Response of tumor to previous chemotherapy and/or radiation therapy will be reported. Several systems for tumor response have been advocated, and a modified Ryan scheme is suggested by the CAP/AJCC, which has been shown to provide good interobserver reproducibility and provide prognostic significance in rectal cancer [26]. Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

- No viable cancer cells (complete response, score 0)
- Single cells or rare small groups of cancer cells (near complete response, score 1)
- Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
- Extensive residual cancer with no evident tumor regression (poor or no response, score 3)

### 8.1.3 R0 Assessment

Margins include the proximal, distal, and radial margins. The radial margin represents the adventitial soft tissue margin closest to the deepest penetration of residual tumor. The distance from the tumor edge to the closest resection margin(s) will be measured and reported. Microscopic involvement of tumor directly at the resection margin (‘‘tumor transected’’) will be reported and is defined as (R1).

## 8.2 Disease Surveillance

After completion of planned treatments, all subjects will be followed with active surveillance to monitor for recurrence. Patients will undergo surveillance scans every 16 weeks during the first 12 months after adjuvant therapy completion. Patients may also undergo endoscopic procedures as clinically indicated. Recurrence is defined as the appearance of one or more new lesions, which can be local, regional, or distant. Disease recurrence may be documented with either radiological findings of recurrent disease or pathological assessment, whichever is available first. Biopsies are recommended, but not required, to confirm recurrent disease. Locoregional recurrences can be detected with endoscopic procedures and biopsies. Disease free survival is defined as the time period from completion of adjuvant therapy till the finding of recurrent disease or death, whichever comes first.

## 8.3 Surgical Outcomes

All patients will be followed post-operatively. Any delays of planned surgery or surgical complications will be recorded. Rates of surgical complications will be compared to the historical controls from our institution.

# 9. CORRELATIVE STUDIES

## 9.1 Correlative Objectives

1) To correlate PD-L1 staining with clinical and biomarkers of response.
2) To evaluate changes in tumor infiltrating lymphocytes following treatment with avelumab and chemoradiation.
3) To characterize the immune infiltrate following treatment with avelumab and chemoradiation.
4) To determine the pretreatment versican proteolysis phenotype and correlate with clinical outcomes and changes in the immune contexture.
5) To collect and bank tissues for future investigations.

## 9.2 Correlative Studies

All of the correlative studies will be performed in Dr. Deming's laboratory. Twenty FFPE slides will be needed for the proposed correlates.

### 9.2.1 PD-L1 Immunohistochemistry (IHC)

PD-L1 staining has been the best studied of all immune biomarkers in the setting of checkpoint blockade. The presence of PD-L1 has been associated with an enhanced treatment benefit rate to checkpoint blockade in many settings. Standardized protocols have now been developed for anti-PD-L1 immunohistochemistry (IHC). Pre-treatment PD-L1 staining will be performed on the pre-treatment biopsy tissue. This staining will be scored as the percent of positive staining cells per high power field (hpf).

### 9.2.2 Tumor Infiltrating Lymphocytes and Examination of the Immune Context

Multiple investigations have now demonstrated a correlation between the presence of tumor-infiltrating lymphocytes (TILs) in cancer tissue and a favorable prognosis. An increase in TILs is commonly being used as a surrogate marker for the development of an immune response in the setting of immune-based anti-cancer therapies. As part of this clinical trial, the presence of TILs and other immune cell populations will be determined, comparing pretreatment biopsy tissue and the resection specimen following avelumab in combination with chemoradiation.

IHC studies will be performed on formalin-fixed/paraffin-embedded tumor tissue. IHC will be performed per standardized protocols for CD3, CD4, CD8, CD20 and CD45RO and potentially other biomarkers of response. Omission of the primary antibody will be used as a negative control along with positive control tissue. Semi-automated quantitative brightfield assessment of expression will be performed using the Vectra imaging system (PerkinElmer) and inForm analysis software system. A scanning protocol will be generated based on the tissue size and location of the cancer within the sample. Biomarker quantification will be calculated as a continuous variable (mean optical density) and also as quartiles (ex. 0, 1+, 2+, or 3+).

### 9.2.3 Versican Proteolysis

Versican (VCAN) is a tumor matrix proteoglycan with known immunoregulatory properties that when cleaved by ADAM-TS proteases releases an immunostimulatory fragment, versikine. Tumors displaying a VCAN proteolysis predominant phenotype (low staining for VCAN and intense staining for versikine) have been shown to have a greater CD8+ T cell infiltration. In these investigations VCAN proteolysis will be examined as an immune biomarker. IHC will be performed for the total (intact) VCAN and versikine. Biomarker quantification will be performed in quartiles (0, 1+, 2+, or 3+). The VCAN proteolysis predominant phenotype will be classified as VCAN $<2+$ and versikine $\geq 2+$.

## 9.3 Sample Collection and Banking

If the subject agrees, leftover samples will be banked for future research. The link connecting subject information and coded samples will be held by the GI research staff and will be accessible to the UWCCC biobank. The Deming Laboratory staff will not have access to this information. Subjects may withdraw any unused samples from the optional banking by contacting the principal investigator.

### 9.3.1 Pretreatment Specimen Collection

A total of 10 formalin fixed paraffin embedded (FFPE) slides from the diagnostic biopsy will be collected and transferred to the Deming Laboratory in the McArdle Laboratory for Cancer Research. These samples will be coded prior to transfer and labeled with the study number, subject ID and date.

### 9.3.2 Resection Specimen Collection

The University of Wisconsin Carbone Cancer Center Biobank will be notified of all subjects undergoing resection as part of this protocol. At the time of the operation, the tissue will be transferred to surgical pathology and residual tissue will be collected by the Biobank staff. Tissue will be then be coded and transferred to Deming Laboratory staff for storage and future studies including but not limited to tissue culture, RNA, DNA and protein analyses. Samples will be coded and labeled with the study number, subject ID and date. In patients with complete pathologic response, tissue sections that include tumor bed/scar (determined by a pathologist) will be submitted for correlative studies.

### 9.3.3 Peripheral Blood Collection

Plasma and serum samples will be collected (50 ml per draw in a heparinized tube green top for plasma and 10 ml per draw in red top tube for serum) as per the study calendar, These samples will then be coded and transferred to the Deming Laboratory for storage and analysis. Samples will be labeled with the study number, subject ID and date.. Collected samples will be used for exploratory studies evaluating potential circulating markers of response. These studies may include, but are not limited to, CD4/CD8 ratio determination, TCR subtyping, cell free tumor DNA evaluation, and measuring serum circulating chemokines and cytokines. The samples will also be banked for future studies.

# 10. STUDY SAFETY ASSESSMENTS

The Principal Investigator (PI) is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

## 10.1 Definitions

### 10.1.1 Adverse Events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can

be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time during treatment and during the 30 day follow-up period. The term AE is used to include both serious and non-serious AEs.

### 10.1.2 Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization (>24 hours). Hospitalization for a planned procedure, such as feeding tube placement, esophageal stent placement or esophagectomy, is not considered an SAE.
- Results in persistent or significant disability or incapacity
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
- The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to EMD Serono or designee.

## 10.2 Recording of Adverse Events

Non-serious adverse events and SAEs will be collected from the time the study drug is given, throughout the treatment period and up to and including the 30 day follow-up period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 30 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, they must be reported to the FDA and EMD Serono See section 11). In addition, all grades of adverse drug reactions (ADRs, AEs related to study medication) and any AE that results in treatment discontinuation will be recorded as study data on CRFs.

All study-related toxicities/SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE (version 5.0) grade and the maximum CTC grade attained
- Whether the AE is serious or not

- Investigator causality rating against the investigational combination (yes or no)
- Action taken with regard to investigational combination agent
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to criteria listed in Section 9.1.2
- Date of hospitalization
- Date of discharge
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to study drug combination

### 10.2.1 Adverse Events Based on Signs and Symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 10.2.2 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator will use the clinical, rather than the laboratory term (e.g. anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

### 10.2.3 Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis during the study should be considered

as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

### 10.2.4 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 10.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

### 10.2.5 Lack of Efficacy

When there is deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the PI or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

### 10.2.6 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported to EMD Serono or designee within 24 hours from the time site personnel become aware of the death. See section 11.

When reporting a death in the CRF, it will be required to identify which of the following best describes the category of death:

- Toxicity for study medication.
- Radiological disease progression.
- Clinical disease progression.
- Other causes.

Death should be reported in the following manner:

- Death clearly the result of disease progression should be reported and should be documented in the eCRF, but it should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 11 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to EMD Serono within the usual timeframes.

# 11. DATA AND SAFETY MONITORING PLAN

## 11.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol PI of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

## 11.2 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCCC monitoring requirements for trials without an acceptable external DSMB are as follows:

### 11.2.1 Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a quarterly basis by the study team for review by the DSMC.

## 11.3 Serious Adverse Event – Reporting within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The PI notifies all investigators involved with the study at the UWCCC, the IRB, and the funding agency and provides documentation of these notifications to the DSMC. For this trial, since the UW PI serves as the sponsor-investigator, the PI will review the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

See Section 12 for detailed instructions on SAE reporting.

## 11.4 Serious Adverse Event – Reporting within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The PI notifies all investigators involved with the study at the UWCCC, the IRB, and the funding agency and provides documentation of these notifications to the DSMC.

The PI will also review the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

See Section 12 for detailed instructions on SAE reporting.

## 11.5 Sponsor-Investigator Responsibilities for SAE Review

For this clinical trial, the UWCCC PI is acting as the Sponsor-Investigator (i.e., the PI holds the IND). As such, the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study. SAE with

suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the UWCCC PI to the FDA and all participating investigators on the study within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study drug will be reported by the UWCCC PI to the FDA and all participating investigators on the study within 7 calendar days.

Refer to Section 12.3.1 for UWCCC PI instructions for reporting to the FDA.

## 11.6 Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports if available and any other pertinent study-related information

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to EMD Serono and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

# 12. EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 2 below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to section 12.1.

**Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1,2].**

**Table 2. FDA Reporting Requirements.**

**FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)**

**NOTE:** Investigators **MUST** immediately report to the University of Wisconsin Carbone Cancer Center and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An adverse event is considered serious if it results in ANY of the following outcomes:

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

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

| Hospitalization | Grade 1 and Grade 2 Timeframes | Grade 3-5 Timeframes |
|---|---|---|
| **Resulting in hospitalization ≥ 24 hrs** | 10 Calendar Days | 24 Hour; 5 Calendar Days |
| **Not resulting in Hospitalization ≥ 24 hrs** | Not required | |

**Expedited AE reporting timelines are defined as:**

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

## 12.1 SAE Requiring [24] Hour Reporting Occurs at UWCCC

### 12.1.1 Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://kb.wisc.edu/uwccc) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports**. A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a. saenotify@uwcarbone.wisc.edu

b. UWCCC PI: Nataliya Uboha, MD, PhD

c. UWCCC PM: Renae Quale

d. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

### 12.1.2 Reporting to EMD Serono

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. Dr. Uboha will assume responsibility for submitting the reportable event(s) to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.

- **Serious Adverse Events**
- **Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)**
- **Occupational exposure (even if not associated with an adverse event)**
- **Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.**

**Contact information for submission of reportable events to EMD Serono:**

**Fax:** +49 6151 72 6914

OR

**E-mail:** GlobalDrugSafety@merckgroup.com

**Specifying:**

- PROTOCOL Number and/or Title
- EMD Serono assigned Study Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

#### 12.1.3 Report to the IRB

Consult the UW-IRB website for reporting guidelines.

## 12.2 SAE Requiring [10] Day Reporting Occurs at UWCCC

#### 12.2.1 Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://kb.wisc.edu/uwccc) for specific instructions on how and what to report to the UWCCC for [10] day reports.

For this protocol, the following entities are required to be notified:

a. saenotify@uwcarbone.wisc.edu

b. Any appropriate parties listed on SAE Routing form

#### 12.2.2 Report to the Sponsor:

See section 12.1.2 - SAEs must be reported to EMD Serono or designee within 24 hours.

#### 12.2.3 Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

## 12.3 Other Reporting Requirements

#### 12.3.1 Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

# 13. ETHICAL AND REGULATORY REQUIREMENTS

## 13.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

## 13.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to EMD Serono Inc. and/or allow EMD Serono Inc., a regulatory authority, or Institutional Review Board (IRB) access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

## 13.3 Ethics and regulatory review

### 13.3.1 Informed consent

Provision of written Informed Consent will be obtained prior to any study-related procedures. The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects will also be notified that they are free to discontinue from the study at any time. The subject will be given the opportunity to ask questions and allowed time to consider the information provided. The original, signed written Informed Consent Form will be stored for the duration of the study. A copy of the signed written Informed Consent Form will be given to the subject.

### 13.3.2 Changes to the protocol and informed consent form

In the event that there are any changes to the protocol, these changes will have to be first reviewed by the sponsor-investigator, and then the amendment and updated consent will be submitted for approval by the institutional IRB. Once approved, an amendment to the protocol and consent form will be generated. Subjects will be notified of the protocol changes and will be provided with the updated ICF for their signature. They will also be provided with a copy of the updated ICF for their records. The funding agency (EMD Serono) will also be updated about any changes to the protocol or consent form.

### 13.3.3 Audits and inspections

The PI will monitor the clinical trial for safety. The PI will assess all expedited adverse events and will periodically review all adverse events observed on the trial. UW Carbone Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events will be followed, which are in compliance with 21 CFR 312.32 and 312.22. The clinical trial data consisting of all required observations, AEs, and laboratory data will be entered into a computerized database in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing

conducted by the UW Carbone Cancer Center Office of Protocol Review and Monitoring, which reports to the UW Data and Safety Monitoring Committee (DSMC) Committee. Safety data will be submitted to the DSMC at least once yearly or more often as required by the DSMP. On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Regular meetings will be held to discuss ongoing patient treatment and adverse events.

Expedited SAE reports submitted by the Investigator to FDA will also be copied to relevant institutional safety committees within the timeframes required by UW. These will also be copied to EMD Serono or designee. The Toxicity List, in addition to the Investigator's Brochure, will be used as a reference for reporting any new SAE. Possible actions taken by the PIs or the UW DSMC if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:

1. Revise consent form
2. Amend the protocol
3. Suspend the protocol

All AEs found to be expected or non-serious will be included in the Annual Report to EMD Serono.

# 14. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

## 14.1 Sample Size and Power Calculation

### 14.1.1 Part 1- Run-in Phase

A total number of 6 subjects will be enrolled during the run-in phase of the trial. A sample size of 6 is sufficient to estimate the true dose limiting toxicity rate of the proposed avelumab/chemoradiation therapy with adequate accuracy. Specifically, the true dose limiting toxicity rate will be estimated with a standard error of 20%.The proposed treatment combination will be considered as safe if dose limiting toxicities are observed in at most 1 patient. The following table shows the probabilities that dose limiting toxicities are observed in at most one patient for various toxicity rates.

**Table 7**: Operating Characteristics of run-in phase – probabilities that the proposed avelumab/chemoradiation therapy will be considered as safe for various true dose limiting toxicity rates ranging between 0.05 and 0.30.

| | True DLT rate | | | | | |
|---|---|---|---|---|---|---|
| | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 | 0.30 |
| Probability that DLTs are observed in at most one patient (treatment combination will be declared as safe) | 0.97 | 0.89 | 0.78 | 0.66 | 0.53 | 0.42 |

For example, if the true DLT rate is 10%, then the probability that the proposed treatment will be declared as safe is 89%.

### 14.1.2 Part 2 – Expansion Phase

This is a Phase 2 portion of the trial, which will evaluate the efficacy of the proposed avelumab/chemoradiation therapy in patients with stage II/III resectable esophageal cancer. The primary endpoint for the phase II component is the pathological complete response rate. A pathological complete response rate of 29% (95% CI: 23-37%) has been reported for standard preoperative chemoradiotherapy [3]. A pathological complete response rate of 20% or less, i.e., less than the lower 95% confidence bound of the reported response rate for standard care, will be considered as unacceptably low for this patient population. It is hypothesized that the co-administration of avelumab with chemoradiation will substantially increase pathological complete response rate to 40% or above. A single-stage design will be used to evaluate the pathological response rate. The null hypothesis that the pathological complete response rate is at most 20% versus will be tested against the alternative hypothesis that the rate it greater than 20%. With a sample size of 24 patients, an anticipated pathological response rate of 40% will be detected with 80% power at the one-sided 0.1 significance level. The following table shows the operating characteristics of the two-state study design.

**Table 8**: Operating characteristics of single-stage study design for expansion cohort.

| | True Pathological Complete Response Rate | | | | | |
|---|---|---|---|---|---|---|
| | 25% | 30% | 35% | 40% | 45% | 50% |
| Probability that the proposed avelumab/chemoradiation therapy will be declared as effective (rejecting the null hypothesis that the pathological complete response rate is at most 20%) | 0.23 | 0.44 | 0.64 | 0.81 | 0.91 | 0.97 |

For example, if the true pathological complete response rate is 45%, then the probability of declaring the proposed avelumab/chemoradiation therapy was effective is 91%.

## 14.2 Analysis Plan

### 14.2.1 General

Descriptive statistics will primarily be generated to summarize the data. For continuous variable, descriptive statistics may include the number of subjects reflected in the calculation (n), mean, standard deviation, median, minimum, and maximum; frequencies and percentages may be displayed for categorical data (e.g., toxicities, responses). Data analysis will be performed using SAS® (SAS Institute Inc., Cary, North Carolina) version 9.4.

### 14.2.2 Demographics

All demographic variables (e.g., gender, age, weight, etc.) will be summarized by standard descriptive statistics, i.e., in terms of means, standard deviations, medians, and ranges for variables on a continuous scale, and in terms of frequency tables for variables on a categorical scale.

### 14.2.3 Primary Endpoints

Part 1: All patients who receive at least one dose of avelumab will be evaluated for toxicity and tolerability. Toxicities observed will be summarized in terms of types and severities by Common Terminology Criteria for Adverse Events (CTCAE) v 45.0. The number and severity of toxicity incidents will be analyzed descriptively in tabular format. The 90% confidence interval for the dose limiting toxicity rate (DLT) will be constructed using the Wilson score method.

Part 2: Pathologic compete response (pCR) is defined as an absence of any viable tumor at microscopic examination of the primary tumor and any lymph nodes sampled after surgery following neoadjuvant therapy. Participants with invalid/missing pCR assessments will be defined as non-responders. The number and frequency of patients with a pCR will be summarized in tabular format. The pCR rate will be reported along with the corresponding 90% confidence interval which will be constructed using the Wilson score method.

### 14.2.4 Secondary Endpoints

Disease free survival (DFS) will be defined as the number of days from the day of resection to the day a subject experiences an event of disease recurrence or death, whichever comes first. If a subject has not experienced an event of disease recurrence progression or death at the time of analysis, then the subject's data will be censored at the date of the last available evaluation. DFS will be summarized using point estimates of the median time to progression and the associated 95% confidence interval. The data will be presented graphically using Kaplan-Meier plots. Incidence of survival complications and the rate of R0 resection will be calculated and report along with the corresponding 95% confidence intervals which will be constructed using the Wilson score method.

# 15. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

## 15.1 Pregnancy

After investigator first becomes aware of its occurrence, he/she should follow the same process for reporting as described for the SAEs.

### 15.1.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, all treatments should be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

### 15.1.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 30 days after the completion of adjuvant therapy. Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

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# APPENDIX A. ECOG PERFORMANCE STATUS.

| ECOG Performance Status | Activity |
|---|---|
| **0** | Fully active, able to carry on all pre-disease performance without restrictions. |
| **1** | Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work. |
| **2** | 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** | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **4** | Completely disabled. Cannot carry on any self-care. 100% confined to bed or chair. |