A single arm, multi-center Phase 2 trial of mFOLFOX6 + trastuzumab + avelumab in first-line, metastatic, HER2-amplified gastric and esophageal adenocarcinomas

Sponsor Investigator
Autumn McRee, MD
The University of North Carolina at Chapel Hill

Statistician
Dominic T. Moore
University of North Carolina at Chapel Hill
dominic_t_moore@unc.edu
Phone: 919-966-8647
Fax: 919-966-4244

Trial Management Provided by
Hoosier Cancer Research Network, Inc.
7676 Interactive Way Suite 120
Indianapolis, IN 46278

Trial Funding & Avelumab Supply Provided by
EMD Serono MS100070

Investigational New Drug (IND) #: 141388

Initial Protocol Version Date: 05NOV2018
Protocol Amendment Version Date:
07JAN2020
29SEP2020

PROTOCOL SIGNATURE PAGE

A single arm, multi-center Phase 2 trial of mFOLFOX6 + trastuzumab + avelumab in first-line, metastatic, HER2-amplified gastric and esophageal adenocarcinomas

VERSION DATE: 29SEP2020

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s)

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

_____

Site Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	A single arm, multi-center Phase 2 trial of mFOLFOX6 + trastuzumab + avelumab in first-line, metastatic, HER2-amplified gastric and esophageal adenocarcinomas
SHORT TITLE	Phase 2 trial of mFOLFOX6 + trastuzumab + avelumab in metastatic, HER2+ gastroesophageal adenocarcinomas
PHASE	II
OBJECTIVES	**Primary Objective** Determine the best objective response rate (CR or PR, bORR) within 24 weeks by RECIST v1.1 in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab **Secondary Objectives** • Determine progression free survival (PFS) by both RECIST v1.1 and iRECIST criteria in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab. • Determine overall survival (OS) in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab. • Determine overall response rate (ORR) at 24 weeks by iRECIST and clinical benefit by the disease control rate (CR or PR or SD) at 24 weeks by both RECIST v1.1 and iRECIST criteria in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab. • Determine the safety and tolerability of avelumab when combined with mFOLFOX6 + trastuzumab. **Exploratory Objectives** Exploratory and correlative studies of tumor genomics and immunology and peripheral lymphocytes.
STUDY DESIGN	Multi-center, single-arm, open-label, Simon's two-stage Phase II clinical trial. Accrual will stop after enrollment of Stage 1 is complete. Total accrual will be 18 subjects.

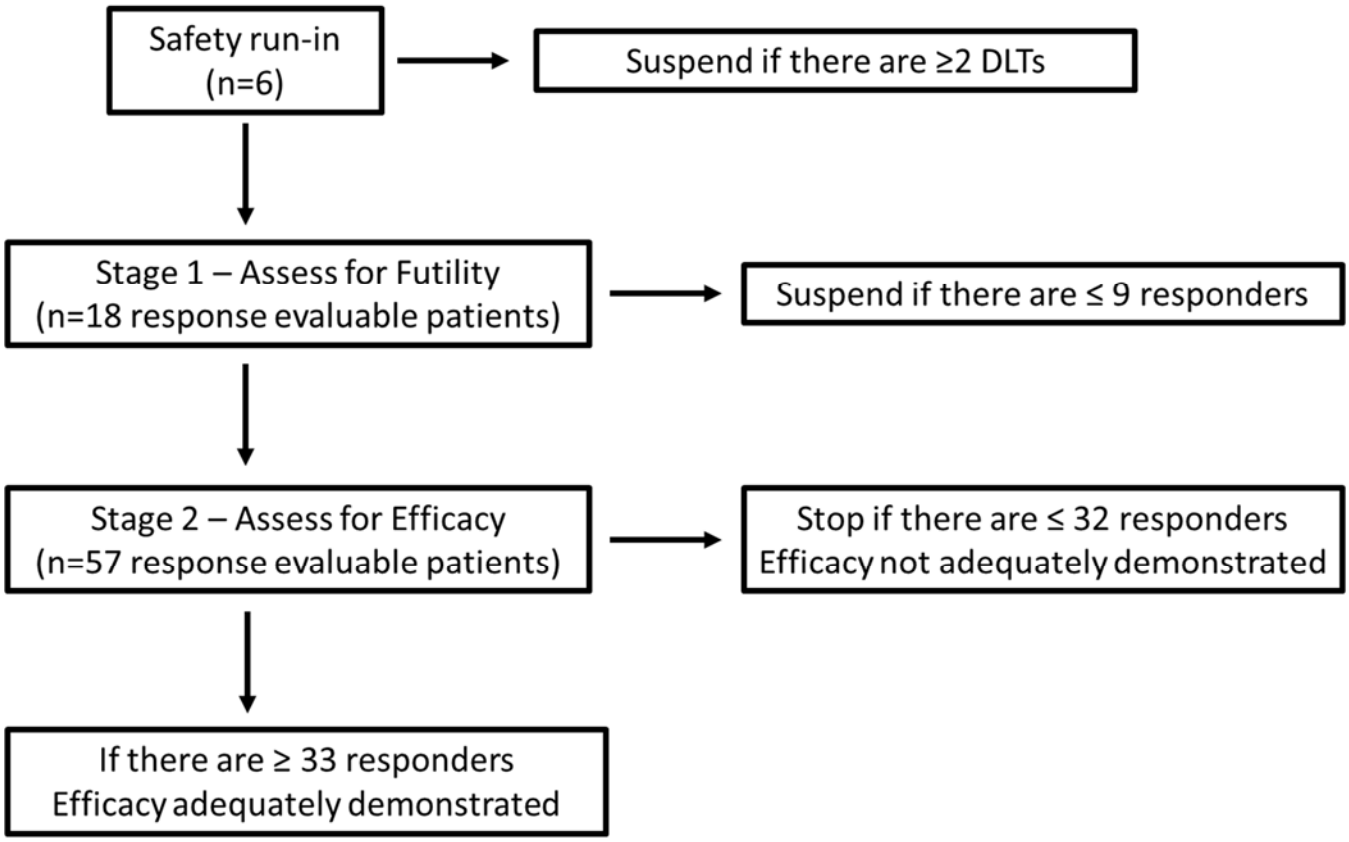
KEY ELIGIBILITY CRITERIA (See Section 3 for complete eligibility criteria)	**Inclusion Criteria** 1. Histologically confirmed esophageal, gastroesophageal junction, or gastric adenocarcinoma that is unresectable or metastatic 2. Age ≥ 18 years at the time of consent. 3. ECOG Performance Status of 0 or 1. 4. HER2 amplification confirmed by prior standard of care testing of tumor specimen (3+ by immunohistochemistry, or 2+ on IHC with ISH with HER2/CEP17 ratio ≥2). 5. Radiographically measurable disease per RECIST 1.1. 6. Adequate organ function within 14 days prior to registration. • ANC ≥ 1.5 x 10^9/L • Hemoglobin ≥ 9 g/dL (may be transfused) • Platelets ≥ 100 x 10^9/L • Creatinine clearance ≥ 30 mL/min OR serum creatinine ≤ 1.5 × ULN • Bilirubin ≤ 1.5 × ULN • AST ≤ 2.5 × ULN • ALT ≤ 2.5 × ULN 7. Left ventricular ejection fraction (LVEF) ≥ 50% or above the lower limit of the institutional normal range, whichever is lower. **Exclusion Criteria** 1. Previous systemic therapy for stage IV disease. **NOTE**: may have received up to one cycle of mFOLFOX6 while HER2 status was pending prior to start of study treatment within the 4 weeks prior to registration. 2. Active infection requiring intravenous systemic therapy. 3. Pregnant or breastfeeding. 4. Prior immune checkpoint inhibitor therapy, or HER2-directed therapy 5. Evidence of interstitial lung disease or active, non-infectious pneumonitis 6. Untreated brain metastasis or brain metastasis treated within 4 weeks prior to enrollment. 7. Known additional malignancy that is active and/or progressive requiring treatment 8. Serious cardiovascular event within 6 months prior to study entry. 9. History of organ allograft, allogeneic stem cell transplantation, immunodeficiency, or is receiving systemic steroid therapy or other immunosuppressive therapy within 7 days before first dose of investigational treatment. 10. Known HIV, HBV, or HCV infection. 11. Active autoimmune disease requiring systemic therapy in the past 3 months. 12. Persisting toxicity related to prior therapy (NCI CTCAE v5 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.

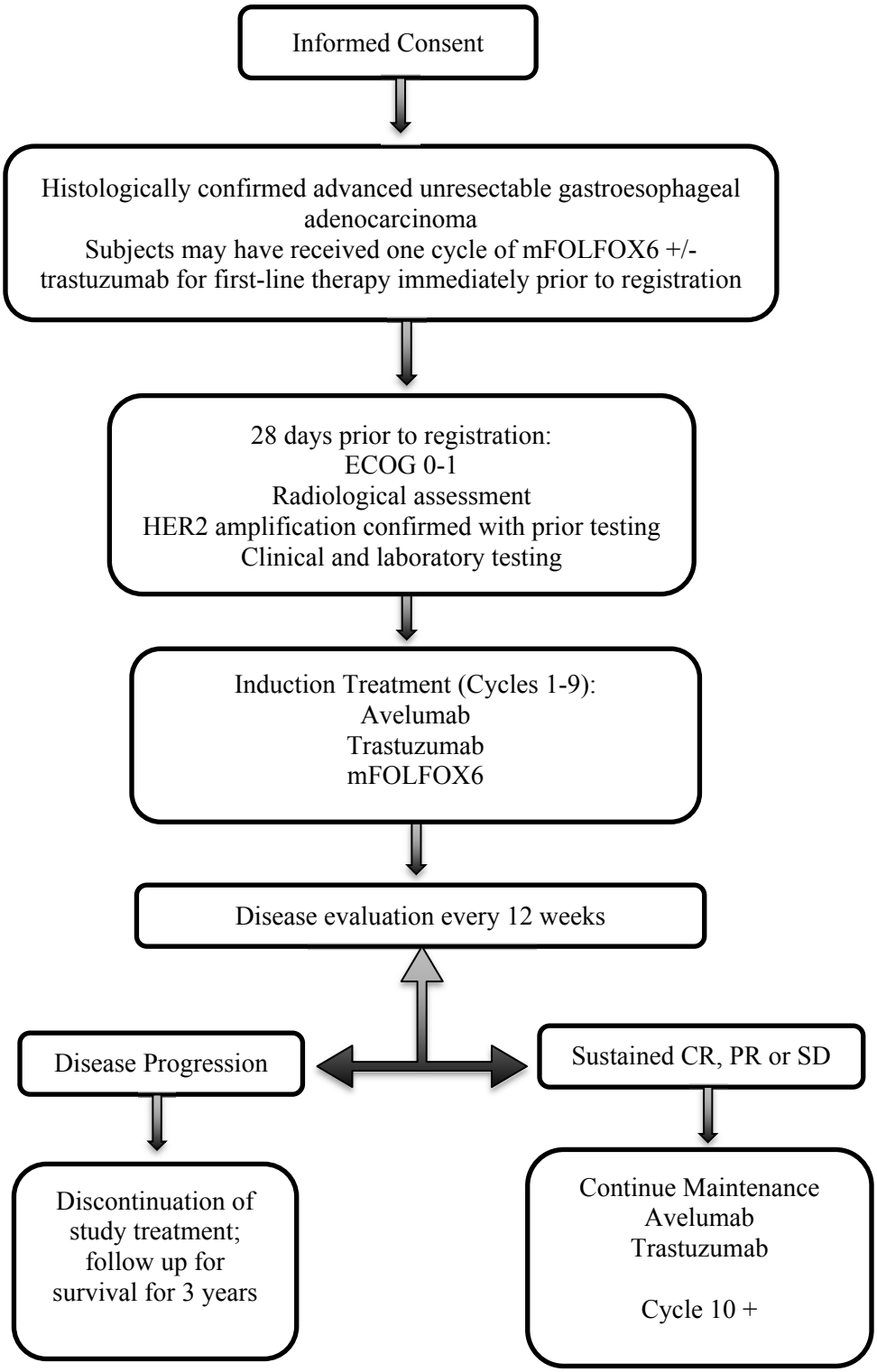
STATISTICAL CONSIDERATIONS	This study will be a prospective, open-label, single arm, multi-center phase 2 clinical trial of mFOLFOX6 + trastuzumab + avelumab in first-line, metastatic, HER2-amplified gastric and esophageal adenocarcinomas. The primary objective of this study is to estimate the best objective response rate (CR or PR, ORR) in these patients within 24 weeks by RECIST 1.1 criteria. Secondary objectives include; estimating PFS by both RECIST 1.1 and iRECIST criteria, estimating OS, estimating the disease control rate (DCR) at 24 weeks by RECIST 1.1 and iRECIST, and characterizing the safety issues associated with this regimen. Exploratory objectives involve investigating various biomarkers and peripheral blood and tumor assays.
TOTAL NUMBER OF SUBJECTS	N = 18
ESTIMATED ENROLLMENT PERIOD	Estimated 22 months
ESTIMATED STUDY DURATION	Estimated 36 months until primary analysis

TABLE OF CONTENTS

SCHEMA

Accrual will halt after completion of enrollment of Stage 1 (18 subjects)




Informed Consent
Histologically confirmed advanced unresectable gastroesophageal adenocarcinoma
Subjects may have received one cycle of mFOLFOX6 +/- trastuzumab for first-line therapy immediately prior to registration
28 days prior to registration:
ECOG 0-1
Radiological assessment
HER2 amplification confirmed with prior testing
Clinical and laboratory testing
Induction Treatment (Cycles 1-9):
Avelumab
Trastuzumab
mFOLFOX6
Disease evaluation every 12 weeks
Disease Progression
Sustained CR, PR or SD
Discontinuation of study treatment; follow up for survival for 3 years
Continue Maintenance
Avelumab
Trastuzumab
Cycle 10 +

1. BACKGROUND AND RATIONALE

1.1 Disease Background

Gastroesophageal cancer is the fourth most common type of cancer worldwide, and despite advances in the diagnosis and treatment, it remains the world's second highest cause of cancer-related deaths [1]. Locally advanced unresectable and metastatic gastroesophageal cancers are not curable conditions, and the goals of therapy include palliation of symptoms, including malignant dysphagia; improvement of quality of life, and prolongation of survival. Prognosis is generally poor, with a median survival time of 3–5 months with best supportive care and 7–9 months with systemic chemotherapy [2, 3]. Systemic chemotherapy is the mainstay of treatment for these patients. Several cytotoxic agents are active against gastroesophageal cancer, including fluoropyrimidines, platinum agents (cisplatin and oxaliplatin), taxanes (paclitaxel, docetaxel), and irinotecan. Additionally, as it is known that the human epidermal growth factor receptor (EGFR) type 2 (HER2) gene is commonly amplified [4-6] and overexpressed in adenocarcinomas of the stomach, gastroesophageal junction (GEJ), and esophagus and is a potential target for therapeutic intervention. Although the role of HER2 as a prognostic marker in gastric cancer remains an issue of debate, HER2 amplification/overexpression is an important therapeutic target for trastuzumab and is associated with significant improvements in progression-free (PFS) and overall survival [7]. Routine diagnostic testing is now recommended in gastric and GEJ adenocarcinomas based on these findings that led to approval of the drug by the FDA [8] and European Medicines Agency (EMA).

1.2 Current Standard of Care

Patients with newly diagnosed metastatic or unresectable gastric, GEJ, and esophageal adenocarcinomas are typically treated with first-line cytotoxic chemotherapy including fluoropyrimidine and platinum agents. The standard of care also calls for testing these patients' tumors for HER2 amplification and adding the anti-HER2 antibody trastuzumab to fluoropyrimidine and platinum chemotherapy in patients with HER2-amplified advanced esophagogastric adenocarcinoma.

HER2 amplification is found in 32% of esophageal adenocarcinomas[9] and 13% of gastric adenocarcinomas[10]. The phase III ToGA trial established that addition of trastuzumab to fluoropyrimidine/platinum combination chemotherapy significantly improved overall survival (OS) from 11.1 months to 13.8 months and response rate from 35% to 47%[7], establishing trastuzumab-based chemoimmunotherapy as the first-line standard of care in these patients. However, patients do invariably develop disease progression, with median progression-free survival of 6.7 months in the ToGA trial, and so therapies that extend the duration of benefit or provide chance at durable response are needed.

1.3 Investigational Treatment

Recent clinical trials have demonstrated the efficacy of immune checkpoint inhibitors in metastatic gastroesophageal cancers, but the optimal biomarkers for patient selection and strategies to optimize efficacy of therapy remain unclear. Notably, in biomarker-unselected refractory gastroesophageal cancer patients, response rates have been roughly 11-12% with nivolumab in the ATTRACTION-2 and CHECKMATE-032 trials of nivolumab[25-27] and the KEYNOTE-059 trial of pembrolizumab[28]. However, studies have varied regarding

improvement in overall survival, with nivolumab improving median overall survival (OS) compared to placebo in an Asian population [26] but avelumab reportedly failing to improve median OS compared to investigator's choice chemotherapy in a global population. Thus, the majority of patients do not derive substantial benefit from immune checkpoint inhibitor monotherapy in this refractory setting. Positive immunohistochemistry for PD-L1 within tumor cells, lymphocytes, or macrophages using the Dako 22C3 antibody, found in 55% of patients, enriched for patients who responded to pembrolizumab in the KEYNOTE-059, improving response rate among microsatellite stable or unknown subjects to 13.3%, and accelerated approval was granted for pembrolizumab in refractory gastric or GE junction PD-L1+ adenocarcinomas. Nevertheless, further improvement in biomarkers and strategies to potentiate the immune response and efficacy of immune checkpoint therapy in more subjects for a longer duration are needed.

There is significant rationale for combining immune checkpoint antibodies with HER2-directed therapy like trastuzumab. Preclinical studies demonstrated that anti-HER2 antibody therapy requires an intact immune system, including IFN-γ secreting CD8+ T-cells, for efficacy, and in mouse models of HER2-amplified breast cancer, co-treatment with anti-HER2 and anti-PD1 antibodies caused significant tumor regression[11]. The immune response to trastuzumab was significantly associated with improved responses in HER2-positive breast cancers, providing further evidence that a major mechanism of trastuzumab's efficacy is harnessing the adaptive immune response [12]. Importantly, in HER2-amplified gastroesophageal cancer models, cytotoxic T lymphocytes directed against HER2 also depend on intact tumoral cellular antigen-processing machinery [13]. Chemotherapy can also facilitate tumor antigen presentation and immune response, including reports of humoral immune responses after 5-fluorouracil[14] or oxaliplatin-based chemotherapy regimens [15, 16]. Moreover, HER2-amplified gastroesophageal cancers have significantly greater expression of PD-L1 [17, 18]. Many ongoing clinical trials of immune checkpoint inhibitors in gastroesophageal cancers, including all the key ongoing first-line trials with chemotherapy (i.e. KEYNOTE-062, JAVELIN Gastric 100), exclude HER2-amplified patients. Thus, HER2-amplified patients represent an understudied cohort within the increasingly crowded gastroesophageal cancer space.

To potentiate benefit with anti-HER2 therapy, it would be ideal to administer immune checkpoint antibodies with first-line therapy, as there is no clear role for continuation of HER2-directed therapy after progression. Several post-progression studies have been negative, including the second-line TYTAN trial of lapatinib [19] and the GATSBY trial of second-line T-DM1 vs. taxane [20]. Though mechanisms of resistance remain unclear, data from a single institution indicates that 35% of patients with a repeat biopsy post-progression indeed had lost HER2 positivity [21]. This would not be surprising given that there is marked intratumoral heterogeneity of HER2 staining even at diagnosis [22], and so outgrowth of HER2-nonexpressing subclones under the selective pressure of anti-HER2 antibody is not unexpected. However, there is emerging data that targeted therapies increase tumor antigen presentation and can potentiate the antitumor adaptive immune response, motivating combinations of targeted therapies with immune checkpoint inhibitors. Indeed, combining BRAF and MEK inhibitors with anti-PD1 therapy is effective in a mouse model of BRAF mutant melanoma[23] and is being studied in several early phase clinical trials[24]. Indeed, this work is now being extended into GI cancers, with ongoing promising trials combining atezolizumab and cobimetinib in

microsatellite stable colorectal cancer, suggesting that paired MAPK inhibition with immune checkpoint inhibitor antibodies is a promising strategy. Thus, in patients with HER2-amplified gastroesophageal cancers, unleashing an amplified antitumor adaptive immune response through administration of immune checkpoint inhibitors with first-line trastuzumab and chemotherapy may provide a more durable response and may have greater likelihood of success than combining immune checkpoint inhibitors with HER2-directed therapy in the second-line setting.

The combination of chemotherapy with FOLFOX and immune checkpoint inhibitors is undergoing testing in a variety of indications but has generally been well tolerated. Notably, combinations of capecitabine, cisplatin, trastuzumab, and pembrolizumab are also starting clinical evaluation (NCT02954536, NCT02901301), reflecting the promise of this strategy. Notably, a combination of 5-fluorouracil and oxaliplatin (i.e. FOLFOX) is the preferred systemic chemotherapy for patients with metastatic gastroesophageal cancer, and though in practice clinicians often extrapolate results from trials of cisplatin/capecitabine, there may well be confounding due to the alternative chemotherapy backbone and differential toxicities and supportive care measures (like corticosteroids) that likely need to be employed with the highly emetogenic cisplatin, as opposed to the less emetogenic oxaliplatin. Several trials have reported on the safety and feasibility of combinations of FOLFOX with PD-1 or PD-L1 antibody therapy, including atezolizumab and pembrolizumab, and multiple studies combining chemoimmunotherapy with PD-1 or PD-L1 antibodies are ongoing, including an ongoing clinical trial of FOLFOX + cetuximab + avelumab in colorectal cancer (NCT03174405). Moreover, combination therapy of trastuzumab with PD-1 antibodies was well tolerated in the PANACEA study, with most common immune-related adverse events of hyper- or hypothyroidism at 6/7% (grade 1-2) and 3.4% pneumonitis (grade 3-4)[29].

1.4 Rationale

Initially we proposed a multi-center single-arm open-label Simon's two-stage Phase II clinical trial of first-line mFOLFOX6 + trastuzumab + avelumab in metastatic HER2-amplified gastric and esophageal adenocarcinomas, following an initial safety run-in of six patients. Archival tissue and longitudinal peripheral blood samples were collected from all patients to facilitate study using UNC's robust immunogenomics translational program and facilities to perform extensive correlative studies to help identify potential biomarkers. Accrual will halt after completion of Stage I (enrollment of 18 patients). Subjects currently on treatment will continue until criteria as defined in Section 6.7 is met.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Determine the best objective response rate (CR or PR, bORR) within 24 weeks by RECIST v1.1 in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab

2.1.2 Secondary Objectives

2.1.2.1 Determine progression free survival (PFS) by both RECIST v1.1 and iRECIST criteria in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab.

2.1.2.2 Determine overall survival (OS) in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab.

2.1.2.3 Determine overall response rate at 24 weeks by iRECIST and clinical benefit by the disease control rate (CR or PR or SD) at 24 weeks by both RECIST v1.1 and iRECIST criteria in first-line treatment of metastatic HER2-amplified gastroesophageal adenocarcinoma patients with the addition of avelumab to mFOLFOX6 + trastuzumab.

2.1.2.4 Determine the safety and tolerability of avelumab when combined with mFOLFOX6 + trastuzumab.

2.1.3 Correlative/Exploratory Objectives

Perform studies of tumor genomics including DNA and/or RNA sequencing to elucidate tumor associated and stromal/immunologic biomarkers of activity and analyze peripheral blood for circulating lymphocyte characteristics and circulating tumor DNA analyses.

2.2 Endpoints

2.2.1 Primary Endpoint

Best Objective Response Rate (bORR): The best objective response rate will be defined as the total number of patients whose best response by 24 weeks are either a CR or PR divided by the number of response evaluable patients

2.2.2 Secondary Endpoints

2.2.2.1 Progression Free Survival (PFS) by RECIST 1.1 will be defined as the time from the start date of treatment to the date of documented progression as determined by RECIST 1.1 or death from any cause. Any patient who has received study treatment but has neither progressed nor died will be censored on the date the patient was known to be alive and progression free.

2.2.2.2 Progression Free Survival by iRECIST (iPFS) will be defined as the time from the start date of treatment to the date of documented progression as determined by iRECIST criteria or death from any cause. Any patient who has received study treatment but has neither progressed nor died will be censored on the date the patient was known to be alive and progression free.

2.2.2.3 Overall Survival (OS) will be defined as the time from start of treatment to the date of death. If the patient has not died, survival will be censored on last date the patient was known to be alive.

2.2.2.4 Disease Control Rate (DCR) used to help determine clinical benefit will be defined as the total number of patients whose best responses are either a CR, PR, or SD divided by the number of response evaluable patients. Patients with best response of SD will need to maintain SD by 24 weeks to be considered to have received clinical benefit from the treatment regimen

2.2.2.5 Safety and tolerability will be assessed by adverse events using CTCAE version 5.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0 or 1.

4. Histologically confirmed esophageal, gastroesophageal junction, or gastric adenocarcinoma, with unresectable or metastatic disease documented on diagnostic imaging studies.

5. HER2 amplification confirmed by prior standard of care testing of tumor specimen (3+ by immunohistochemistry, or 2+ on IHC with ISH with HER2/CEP17 ratio ≥2).

6. Radiographically measurable disease according to RECIST 1.1 within 28 days prior to registration.

7. Adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5 x 10^9/L
Hemoglobin (Hgb)	≥ 9 g/dL (may have been transfused)
Platelets	≥ 100 x 10^9/L OR ≥ 75 x 10^9/L for patients who received Cycle 1 of mFOLFOX6 +/- trastuzumab prior to registration
Renal	
Calculated creatinine clearance[1]	≥ 30 mL/min
OR creatinine	≤ 1.5 × upper limit of normal (ULN)

Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN) (Subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL, if their conjugated bilirubin is < 1.5× ULN)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN OR ≤ 5x ULN in patients with known liver metastases
Alanine aminotransferase (ALT)	≤ 2.5 × ULN OR ≤ 5x ULN in patients with known liver metastases

[1] Cockcroft-Gault formula will be used to calculate creatinine clearance (See Appendix B). Only needs to meet one criterion for renal inclusion criterion.

10. Left ventricular ejection fraction (LVEF) ≥ 50% or above the lower limit of the institutional normal range, whichever is lower.

11. Females of childbearing potential must have a negative serum pregnancy test at screening. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

12. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 7 months (210 days) after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

13. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Previous systemic therapy for stage IV disease – EXCEPT that patient may have received one cycle of mFOLFOX6 +/- trastuzumab within the 4 weeks prior to registration.

2. Active infection requiring intravenous systemic therapy.

3. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

4. Treatment with any investigational drug within 28 days prior to registration.

5. Prior immune checkpoint inhibitor therapy (i.e. anti-CTLA-4, anti-PD-L1, anti-PD-1), or HER2-directed therapy (including trastuzumab)

6. Evidence of interstitial lung disease or active, non-infectious pneumonitis

7. Untreated brain metastasis or brain metastasis treated within 4weeks prior to enrollment.

8. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least five years.

9. Serious cardiovascular event within 6 months prior to study entry, including myocardial infarction, malignant hypertension, severe/unstable angina, symptomatic congestive heart failure (≥ New York Heart Association Classification Class II), cerebral vascular accident, transient ischemic attack, or serious cardiac arrhythmia requiring medication.

10. History of organ allograft or allogeneic stem cell transplantation

11. Active autoimmune disease requiring systemic treatment in the past 3 months (for example with disease modifying agents, corticosteroids, or immunosuppressive drugs). Exceptions Include:
    - Subjects with endocrine diseases stable on replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) or hormone suppression.
    - Subjects that require intermittent use of bronchodilators, local steroid injections, or inhaled or topical steroids
    - Subjects with vitiligo, psoriasis, Sjogren's syndrome, or resolved childhood asthma/atopy

12. 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).

13. Known history of testing positive for HIV or known acquired immunodeficiency syndrome.

14. Known history of Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection will be permitted.

15. Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines.

16. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5 Grade ≥ 3).

17. Persisting toxicity related to prior therapy (NCI CTCAE v5 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.

18. 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 informed consent, the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy **within 28 days** of registration.

5. TREATMENT PLAN

The initial intent of the study was to be a multi-center single-arm open-label Simon's two-stage Phase II clinical trial of first-line mFOLFOX6 + trastuzumab + avelumab in metastatic HER2-amplified gastric and esophageal adenocarcinomas.

Accrual will halt after completion of Stage I (enrollment of 18 patients). This decision is not due to safety issues. Subjects currently on treatment will continue until criteria as defined in Section 6.7 is met.

5.1 Treatment Administration for Induction

The order of administration for study treatment during induction is avelumab, trastuzumab then mFOLFOX6. Subjects should receive 9 cycles of induction therapy with avelumab, trastuzumab, and mFOLFOX6, regardless of whether they received a cycle of mFOLFOX6 +/- trastuzumab immediately prior to registration. If a cycle of mFOLFOX6 +/- trastuzumab is given prior to registration, loading dose of trastuzumab will not be repeated.

An infusion window of ± 10 minutes may be applied to the avelumab. Institutional standards for infusion and infusion window may be applied to trastuzumab and mFOLFOX6. Body surface area (BSA) should be recalculated for change in weight based on institutional standards. A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

Drug	Dose	Route	Schedule	Cycle Length
INDUCTION (Cycles 1-9)				
Avelumab	800 mg	Intravenously (IV) over 60 minutes	Day 1 of Cycles 1-9	14 days
Trastuzumab	6 mg/kg loading dose	IV (e.g. over 90 min)	Day 1 of Cycle 1	
Trastuzumab	4 mg/kg	IV (e.g. over 30 min)	Day 1 of Cycles 2-9	
Oxaliplatin	85 mg/m^2	IV (e.g over 2 hours)	Day 1 of Cycles 1-9	

Leucovorin	400 mg/m^2	IV per (e.g. over 2 hours)	Day 1 of Cycles 1-9	
5-fluorouracil	400 mg/m^2 bolus and 2400 mg/m^2	IV bolus and IV infusion (e.g. continuous 46 hour infusion)	Day 1 of Cycles 1-9	

5.2 Treatment Administration for Maintenance

The order of administration for study treatment during induction is avelumab then trastuzumab. An infusion window of ± 10 minutes may be applied to the avelumab. Institutional standards for infusion and infusion window may be applied to trastuzumab. Dose recalculation for change in weight is based on institutional standards. A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

Drug	Dose	Route	Schedule	Cycle Length
MAINTENANCE (Cycles 10-n)				
Trastuzumab	4 mg/kg	IV (e.g. over 30 min)	Day 1 of Cycles 10-n	14 days
Avelumab	800 mg	IV over 60 minutes	Day 1 of Cycles 10-n	

5.3 Safety Lead-In

The study will be designed with a 6-subject safety run-in. If 2 or more subjects have significant toxicities as defined below during the DLT period, study accrual will pause, and the treatment plan will be reassessed and amended as appropriate. Toxicities will be assessed per NCI CTCAE v5. After the sixth subject is enrolled, there will be a pause in further enrollment until the first six subjects have completed two cycles to assess toxicities per NCI CTCAE v5.

5.3.1 Definition of Dose Limiting Toxicity

DLTs are defined as at least as possibly related to study treatment with avelumab, trastuzumab, or mFOLFOX6. If an apparent DLT is clearly due to underlying gastroesophageal adenocarcinoma or is otherwise clearly unrelated to the study treatment, then the investigator will specify that the event is not a DLT. The DLT period consists of the first 2 cycles of treatment.

An event will be considered a DLT per NCI CTCAE criteria v5, if it occurs within the DLT reporting period (i.e., within two cycles of therapy) as specified below:

- Any grade 5 AE
- Grade 4 diarrhea or colitis
- Grade 3 diarrhea or colitis that is refractory to corticosteroids (worsens or persists for more than 5 days despite corticosteroid treatment as described in Section 6.2)
- Grade 4 rash
- Grade 3 rash that recurs despite prior course of corticosteroids
- Grade 3-4 pneumonitis

- Grade 3-4 blood bilirubin increased (total bilirubin >3x ULN)
- AST or ALT increased to >5x ULN if baseline AST and ALT were within normal limits; or AST or ALT increased to >10x ULN if baseline AST and ALT were >1 to 5x ULN
- Immune-mediated myocarditis
- Grade 3-4 infusion related reaction or anaphylaxis
- Grade 4 creatinine increased (>6x ULN)
- Any other immune-related non-endocrine AEs that are Grade 4 or are Grade 3 that recur despite prior course of corticosteroids (excluding alopecia, isolated electrolyte disturbances that responds to correction within 72 hours of onset, isolated amylase or lipase abnormalities that are not associated with symptoms or clinical signs of pancreatitis and decrease to < Grade 4 within 1 week of onset)

5.4 Pre-medication and Hydration for Study Treatment

5.4.1 Avelumab

Premedication: 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 and 500-650 mg paracetamol IV or oral). 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 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), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

5.4.2 Trastuzumab

Premedication, hydration and administration will be provided as per institutional standards per routine care for patients who receive trastuzumab. Please see Section 5.7.2 for information regarding management of infusion reactions. The biosimilar for trastuzumab may be used.

5.4.3 mFOLFOX6

Premedication, hydration and administration will be provided as per institutional standards per routine care for patients who receive mFOLFOX6. For prophylaxis of emesis, premedication with a 5HT3 antagonist is typically administered. Premedication with corticosteroids on Day 1 only may be considered per institutional standard practice.

5.5 Concomitant Medications

5.5.1 Allowed Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of

medical care. Hematopoietic growth factors should not be routinely administered. All concomitant medication and concurrent therapies will be documented at Baseline/Screening and throughout the study as summarized in the Time and Events Table in Section 0. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

5.5.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. The following medications are prohibited while receiving protocol therapy:

- Systemic anticancer or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected immune-related adverse events of interest (irAEIs) or emergent management of serious infusion/allergic reactions. (**NOTE:** Use of inhaled steroids, local injection of steroids, topical steroids, and steroid eye drops are allowed). If medically deemed necessary (eg, acute asthma or chronic obstructive pulmonary disease exacerbation), Investigators are allowed to use their judgment to treat patients with systemic steroids. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of avelumab.
- Live vaccines within 4 weeks prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live viruses are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.

5.6 Supportive Care

5.6.1 Chemotherapy Induced Nausea/Vomiting

This chemotherapy regimen has moderate emetogenicity, and all subjects on study should receive an appropriate prophylactic antiemetic regimen per local standard of care such as a 5HT3 receptor antagonist +/- NK1 receptor antagonist. Corticosteroids may be administered per routine institutional practice on Day 1. Additional corticosteroids on subsequent days are not allowed and alternative antiemetics should be used.

5.6.2 Chemotherapy Associated Diarrhea

Diarrhea that occurs during treatment should be aggressively managed given that diarrhea may be secondary to cytotoxic chemotherapy or may arise as a consequence of autoimmune colitis. Patients should start an anti-diarrheal such as loperamide at the earliest evidence of diarrhea, and should be instructed to take 4 mg loperamide by mouth immediately, followed by 2 mg every 2-4 hours after each unformed stool. Patients should also be instructed to increase intake of clear fluids and to stop ingesting lactose-containing products and alcohol. Patients should be instructed

to monitor stool output closely and monitor for fever, abdominal pain, lightheadedness, and other symptoms concerning for complicated diarrhea.

5.6.3 Reproductive Information

Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of highly effective methods of contraception from the time of informed consent until 7 months (210 days) after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral route, intravaginal route, transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral, injectable, implantable
- Other: Intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence (if the preferred and usual lifestyle)

5.7 Hypersensitivity/Infusion Reactions

5.7.1 Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate 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 avelumab infusion. 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 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. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab 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.

5.7.2 Trastuzumab

Infusion reactions to trastuzumab should be treated per institutional standards. The following measures are suggested for trastuzumab related infusion reaction:

Grade 1-2 infusion related reaction without dyspnea or transient hypotension: Decrease infusion rate to half the rate given at the time of event onset. If symptoms persist, consider temporarily interrupting drug infusion and administering acetaminophen and/or diphenhydramine. After symptoms resolve, may resume infusion at original rate after 30 minutes. For subsequent infusions, may consider adding acetaminophen and diphenhydramine premedication and slowing infusion rate at treating physician's discretion.

Grade 2 infusion related reaction with dyspnea or transient hypotension: Temporarily interrupt drug infusion and administer acetaminophen and/or diphenhydramine. After symptoms resolve, may resume infusion. For subsequent infusions, add acetaminophen, diphenhydramine, and H2 histamine receptor antagonist premedication, and slow infusion rate at treating physician's discretion.

Grade 3-4 infusion related reaction or Grade 3-4 anaphylaxis: Discontinue drug infusion and immediately start supportive management of anaphylaxis and resuscitation. Supportive medications may include antihistamines, epinephrine, bronchodilators, oxygen, and corticosteroids.

5.7.3 Chemotherapy

Infusion reactions to chemotherapy should be treated per institutional standards.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables below, treatment may be delayed ≤ 2 weeks from the expected day of the next treatment for any reason. If treatment is delayed > 2 weeks, subjects will proceed with the next cycle of treatment at the dose level recommended according to the tables below.

6.2 Dose Levels for Dose Reductions

Dose level	5FU Bolus	5FU Infusion	Leucovorin	Oxaliplatin	Trastuzumab (after loading dose)	Avelumab
Starting Dose	400 mg/m^2	2400 mg/m^2	400 mg/m^2	85 mg/m^2	4 mg/kg	800 mg
Dose level (-1)	320 mg/m^2	1920 mg/m^2	400 mg/m^2	65 mg/m^2	4 mg/kg	800 mg
Dose level (-2)	270 mg/m^2	1600 mg/m^2	400 mg/m^2	50 mg/m^2	4 mg/kg	800 mg
Dose level (-3)	230 mg/m^2	1360 mg/m^2	400 mg/m^2	40 mg/m^2	4 mg/kg	800 mg

If a dose reduction beyond level -3 is required for oxaliplatin, oxaliplatin will be discontinued and 5FU/leucovorin+trastuzumab+avelumab will be continued.

If a dose reduction beyond level -3 is required for 5FU, then mFOLFOX6 will be discontinued and trastuzumab+avelumab will be continued

6.3 Dose Modifications for Study Treatment

	Supportive Management	Avelumab Dose Modification	Trastuzumab Dose Modification	mFOLFOX6 Dose Modification (during cycles 1-9)
Diarrhea/Colitis				
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Symptomatic treatment (e.g. loperamide)	Continue avelumab If worsens: Treat as Grade 2, 3 or 4.	Continue	Continue
Grade 2 Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Symptomatic treatment (e.g. loperamide)	Delay starting next cycle until grade ≤1, then resume without any dose reduction. If persists > 5-7 days or recurs: Treat as Grade 3 or 4	Delay starting next cycle until grade ≤1, then resume without any dose reduction.	Delay starting next cycle until grade ≤1, then resume without any dose reduction.
Grade 3 to 4 Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	Withhold avelumab until steroids are tapered off. If event was initially grade 3, may resume avelumab without dose reduction. If event was recurrent grade 3 or grade 4 or diarrhea	Delay starting next cycle until grade ≤1, then resume without any dose reduction.	Delay starting next cycle until grade ≤1, then resume with 5FU and oxaliplatin reduced by one dose level

Grade 4: Life-threatening, perforation	IF IMPROVED Continue steroids until Grade ≤ 1, then taper over at least 1 month; IF WORSENED, PERSISTS >3-5 DAYS, OR RECURS AFTER IMPROVEMENT: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.	/colitis is refractory to corticosteroids, permanently discontinue avelumab		
Rash				
Grade 1-2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids)	Continue avelumab for first instance. However, if persists >1-2 weeks or recurs, withhold avelumab. Consider skin biopsy. Consider 0.5-1 mg/kg/day prednisone or equivalent, and once improving taper steroids over at least 1 month. May resume avelumab after steroid taper completed. If worsens, treat as grade 3-4	Continue	Continue
Grade 3-4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections If improves to Grade ≤ 1: Taper steroids over at least 1 month	Withhold avelumab for Grade 3. May resume avelumab therapy following steroid taper Permanently discontinue avelumab for Grade 4 or recurrent Grade 3	May continue if grade 3 Delay if grade 4	May continue if grade 3 Delay if grade 4

	Supportive Management	**Avelumab Dose Modification**	**Trastuzumab Dose Modification**	**mFOLFOX6 Dose Modification (during cycles 1-9)**
Pneumonitis				
Grade 1: Asymptomatic, radiographic changes only	Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults If worsens, treat as grade 2 or grade 3-4	Consider withholding avelumab therapy	Continue	Continue
Grade 2: Symptomatic (mild to moderate), medical intervention indicated	Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.	Withhold avelumab therapy. May resume avelumab following steroid taper	Withhold trastuzumab therapy. May consider resuming trastuzumab when improved to ≤Grade 1 after discussion with medical monitor.	May continue 5FU/leucovorin or delay until improved to ≤Grade 1. Withhold oxaliplatin until improved to ≤Grade 1.
Grade 3-4 Grade 3: Severe symptoms; New/worsening hypoxia Grade 4: Life-threatening	Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)	Permanently discontinue avelumab	Discontinue trastuzumab	Delay until ≤Grade 1. Discontinue on-protocol therapy. Subsequent therapy at discretion of investigator

	Supportive Management	Avelumab Dose Modification	Trastuzumab Dose Modification	mFOLFOX6 Dose Modification (during cycles 1-9)
Hepatic				
CATEGORY 1 AST or ALT > ULN to 3.0 x ULN (if baseline AST and ALT were normal) OR AST or ALT >3 to 5 x ULN (if baseline AST and ALT were 1 to 3 x ULN) OR AST or ALT > 5 to 8 x ULN (if baseline AST and ALT were >3 to 5 x ULN) OR Total bilirubin > ULN to 1.5 x ULN	If worsens, treat as Grade 2 or Grade 3-4	Continue avelumab	Continue trastuzumab	Continue
CATEGORY 2 AST or ALT >3 to 5 x ULN (if baseline AST and ALT were normal) OR AST or ALT >5 to 10 x ULN (if baseline AST and ALT were >1 to 3 x ULN) OR AST or ALT > 8 to 10 x ULN (if baseline AST and ALT were >3 to 5 x ULN) OR Total bilirubin > 1.5 to ≤ 3 x ULN	Increase frequency of monitoring to every 3 days. If elevation persists >5-7 days or worsens, treat as Category 3	Withhold avelumab If improved to Category 1, resume avelumab and routine monitoring	May continue trastuzumab or delay until Category 1	May continue or delay until Category 1
CATEGORY 3 AST or ALT > 5 x ULN (if baseline AST and ALT were normal) OR AST or ALT > 10 x ULN (if baseline AST and ALT were >1 to 5 x ULN) OR Total bilirubin > 3 x ULN	Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	Permanently discontinue avelumab	Delay until Category 1	Delay until Category 1

	Supportive Management	**Avelumab Dose Modification**	**Trastuzumab Dose Modification**	**mFOLFOX6 Dose Modification (during cycles 1-9)**
Cardiac				
If LVEF decreases ≥16% from baseline or decreases below the lower limit of normal and is ≥10% below baseline, and ASYMPTOMATIC	Check EKG, cardiac enzymes including troponin I or T, CK, and CK-MB. If any abnormality, treat as Suspected myocarditis. If initial workup shows no other abnormalities, repeat echocardiogram or MUGA every 4 weeks. Strongly consider referral to cardiology and initiation of medical therapy for cardiomyopathy, such as beta blockers and angiotensin converting enzyme (ACE) inhibitors.	Withhold avelumab when trastuzumab is held. May resume avelumab if/when trastuzumab is resumed.	Withhold trastuzumab for at least 2 cycles. If LVEF returns to normal limits within 4-8 weeks and remains at ≤15% decrease from baseline value, may resume trastuzumab Discontinue trastuzumab permanently if LVEF remains persistently decreased for >8 weeks or if treatment must be interrupted for cardiomyopathy for more than 3 episodes.	May delay or continue per investigator judgment
Suspected myocarditis - 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.	Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	Withhold avelumab. If symptoms improve and immune mediated etiology is ruled out, and there is no decline in LVEF, resume avelumab therapy. If symptoms improve and immune mediated etiology is ruled out, but there is persistent decline in LVEF, treat as asymptomatic LVEF decline above. 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.	Withhold until myocarditis exonerated If symptoms improve and serious etiology is ruled out, and there is no decline in LVEF, resume trastuzumab therapy. If symptoms improve and immune mediated etiology is ruled out, but there is persistent decline in LVEF, treat as asymptomatic LVEF decline above.	Withhold until myocarditis and 5FU-related cardiotoxicity are exonerated

Immune-mediated myocarditis	Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections. Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).	Permanently discontinue avelumab	Discontinue on-protocol therapy	Discontinue on-protocol therapy
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001				

6.4 mFOLFOX6 Modification

6.4.1 Hematologic Toxicity

For grade 2 neutrophil count decreased on Day 1, delay starting next cycle until grade ≤ 1, then resume without any dose reduction. If delay is two or more weeks or recurrent events occur requiring at least two delays, then subsequently decrease 5FU and oxaliplatin by one dose level.

For grade 3 neutrophil count decreased on Day 1 or grade 2 platelet count decreased, delay starting next cycle until grade ≤1, then resume oxaliplatin with one dose level decreased and resume 5FU without any dose reduction. If delay is two or more weeks or recurrent events occur requiring at least two delays, then decrease 5FU and oxaliplatin by one dose level.

For grade 4 neutrophil count decreased on Day 1 or febrile neutropenia or grade 3-4 platelet count decreased, delay starting next cycle until grade ≤1, then decrease 5FU and oxaliplatin by one dose level.

6.4.2 Nausea/Vomiting

For grade 3-4 nausea/vomiting, delay starting next cycle until grade ≤ 1, then decrease 5FU and oxaliplatin by one dose level.

6.4.3 Sensory or Motor Neuropathy

For grade 2 symptoms persisting for an entire cycle (14 days) or transient grade 3 symptoms that last for < 7 days, continue mFOLFOX6 with one dose level reduction of oxaliplatin for all subsequent cycles.

For grade 3 symptoms persisting for an entire cycle (14 days) or grade 4 symptoms, discontinue oxaliplatin.

For prolonged duration of pharyngolaryngeal dysesthesia, increase duration of oxaliplatin infusion to 6 hours for all subsequent cycles.

6.5 Select Immune Related Adverse Events Requiring Avelumab Dose Delay

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

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. Endocrinology consult if needed 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. 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. Consider hospitalization. Endocrinology consult 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. 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). 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): • 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) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	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. • Add prophylactic antibiotics for opportunistic infections.	
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 If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: 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 **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

6.6 Toxicities Requiring Avelumab Discontinuation

Any toxicities that occur as described below that are deemed related to study therapy with avelumab will mandate discontinuation of protocol therapy. Subjects may subsequently continue on standard of care therapies including mFOLFOX6 +/- trastuzumab per the judgment of the treating investigator and should continue to be followed radiographically until disease progression.

- Grade 4 diarrhea or colitis
- Grade 3 diarrhea or colitis that is refractory to corticosteroids
- Grade 4 rash
- Grade 3 rash that recurs despite prior course of corticosteroids
- Grade 3-4 pneumonitis
- Grade 3-4 blood bilirubin increased (Total bilirubin >3x ULN)
- AST or ALT increased to >5x ULN if baseline AST and ALT were within normal limits; or AST or ALT increased to >10x ULN if baseline AST and ALT were >1 to 5x ULN
- Immune-mediated myocarditis
- Grade 3-4 infusion related reaction or anaphylaxis
- Grade 4 creatinine increased (>6x ULN)
- Any other immune-related non-endocrine AEs that are Grade 4 or are Grade 3 that recur despite prior course of corticosteroids (excluding alopecia, isolated electrolyte disturbances that responds to correction within 72 hours of onset, isolated amylase or lipase abnormalities that are not associated with symptoms or clinical signs of pancreatitis and decrease to < Grade 4 within 1 week of onset)

6.7 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression by RECIST 1.1 with lack of clinical benefit
  - **NOTE** that subjects who are clinically benefiting from therapy may continue on protocol therapy at the discretion of the treating investigator if it is felt to be in the subject's best interest. Subsequent restaging scans must occur within 4-8 weeks to either confirm or refute progression by iRECIST. Subjects who subsequently have further progression confirmed by iRECIST must discontinue protocol therapy.
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥28 days.

6.8 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 14 days	**Screen**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycles 4-9**	**Cycles 10-n**	**30/90 day safety follow up**[12]	**Long-term Follow up**[13]
	-28 days	Day 1[11] ± 3 days	Day 1 ± 3 days	Day 1 ± 3 days	Day 1 ± 3 days	Day 1 ± 3 days	30/90 days (+ 7 days)	Every 3 months (±14 days)
REQUIRED ASSESSMENTS								
Informed Consent	X							
Medical History[1]	X							
HER2, PD-L1 and MSI/MMR results[2]		X						
Physical Exam[14]	X	X	X	X	X	X[14]	D30	
Vital signs and ECOG Performance Status[3]	X	X	X	X	X	X		
Echocardiogram or MUGA scan[4]	X				X[4]	X[4]		
AE and concomitant medication review	X	X	X	X	X	X	X	
LABORATORY ASSESSMENTS								
Complete Blood Cell Count with diff (CBC)	X	X	X	X	X	X	D30	
Comprehensive Metabolic Profile (CMP)	X	X	X	X	X	X	D30	
Magnesium, Phosphate	X	X	X	X	X	X		
Thyroid Function Testing[5]	X				X[5]	X[5]	D30	
Pregnancy test (serum or urine) (WOCBP)[5]	X		X		X[5]	X[5]		
DISEASE ASSESSMENT								
CT of chest[6]	X				X[6]	X[6]		X[6]
CT or MRI of abdomen and pelvis[6]	X				X[6]	X[6]		X[6]
MRI Brain (only if clinically indicated) [6]	X							
TREATMENT EXPOSURE								
Avelumab IV		X	X	X	X	X		
Trastuzumab IV		X	X	X	X	X		
mFOLFOX6 IV		X	X	X	X			
SPECIMEN COLLECTION								
Archival Tumor Tissue[7]	X							
Standard of Care Biopsy Tissue[7]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Correlative Blood Samples[8]		X[8]			X[8]		D30	
Stool for microbiome analysis[9]	X[9]							
BANKING SAMPLES								
Whole Blood[10]		X			X[10]			
Unstained Slides[9] (if available)[10]		X						
Serum and Plasma[10]		X			X[10]		D30	
FOLLOW-UP								
Survival Status, Subsequent Therapy								X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

Key to Footnotes

1. Medical History to include: diagnosis and staging per AJCC staging manual Ed 8 (pathology report, radiology imaging, staging documentation), a smoking history questionnaire and trial awareness question. Prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc), radiation therapy, or surgery.

2. HER2 amplification confirmed by prior standard of care testing of tumor specimen (3+ by immunohistochemistry, or 2+ on IHC with ISH with HER2/CEP17 ratio ≥2) is required for eligibility. Consensus guidelines from NCCN recommend testing for PD-L1 expression using the Combined Positive Score (CPS) and testing for microsatellite instability/deficient mismatch repair status for metastatic gastric or gastroesophageal cancer. This testing, if not already done, should be requested and performed per standard of care and results reported when available. Results do not need to be available and reported in any specific timeframe, and if testing is requested but is not successfully performed, this would not comprise a deviation.

3. Vital signs to include blood pressure, heart rate, resting oxygen saturation, weight, and height (screening only) and ECOG performance status.

4. Echocardiogram or MUGA scan should be performed at screening, then every 6 cycles (Cycle 6, Cycle 12 and on). The same modality should be used over the duration of the study.

5. Thyroid Function testing should be performed at screening, then every 3 cycles (Cycle 4, Cycle 7, Cycle 10 and on) and at safety visit (if not performed in the previous 8 weeks). TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator. Serum β-HCG must be performed at screening for women of child-bearing potential. The test result must be confirmed as negative prior to dosing with study medication. A serum or urine pregnancy test must be repeated every 4 weeks while receiving study medication.

6. Radiological assessments should be done within 4 weeks prior to Cycle 1 Day 1 of treatment. Tumor imaging should remain consistent throughout study, and should include those thought by investigator to best capture status of disease. Disease assessments should include contrasted computed tomography (CT) of the chest and either contrasted CT of abdomen and pelvis or MRI of abdomen and pelvis. Repeat tumor imaging every 12 weeks (± 1 week). During long term follow up, radiology imaging should be performed per institutional standards. **NOTE**: Subjects who have progression per RECIST 1.1 but are clinically well may continue on therapy per investigator discretion per Section 6.4 but should have repeat scans 4-8 weeks later. If subject does not have iCPD, then scans should resume every 12 weeks (± 1 week). MRI of the brain should only be done if clinically indicated.

7. Archival tissue will be requested during screening and is required if available. If archival tissue is not available, a new biopsy is not required and the subject may still be eligible. If a biopsy is done for standard of care purposes at any point after registration, tissue for correlative analysis will be requested and subject consent will be obtained. Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status. See Correlative Laboratory Manual (CLM) for details regarding this sample collection.

8. Blood samples for correlative analysis will be collected prior to treatment on Cycle 1 Day 1 (C1D1), at first disease evaluation (roughly after Cycle 6) and at progression/D30 safety visit. Samples collected for correlative analysis will include: samples for ctDNA analysis and PBMCs for flow cytometry. See CLM for details regarding this collection.

9. Stool will be collected for microbiome analysis within the 28 days prior to the start of treatment on C1D1 after the subject has been registered to the study. See CLM for details regarding this collection.

10. Whole blood for banking is to be collected at Pre-Treatment C1D1 and at first disease evaluation (roughly after Cycle 6). Submission of unstained slides for banking from an archived FFPE tumor block (if available). Serum and plasma for banking are to be collected at Pre-Treatment C1D1, at first disease evaluation (roughly after Cycle 6) and at progression/30-Day Safety Follow up visit. See CLM for collection, labeling, processing, and shipping instructions.

11. C1D1 labs obtained within 7 days prior to study drug administration do not need to be repeated.

12. The safety visit should only occur when subjects permanently stop study treatment, around 30 days (+7 days) after last dose of study drug. The Day 90 safety follow up may be accomplished via email, phone call or communication with local physician.

13. Subsequent long term follow-up will occur in all subjects until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed after their D90 safety visit for disease progression every 3 months for 3 years. Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 3 years from the time of documented progression (±14 days). Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Long term survival follow up will be limited to history of any subsequent cancer treatments, an assessment of any SAEs (including checking for pregnancy) considered to be possibly or probably related to study treatment until resolution, and survival status.

14. During the maintenance period, a physical exam may be performed every other cycle beginning with Cycle 10. All other assessments will be performed as outlined in the calendar prior to each cycle and a member of the research staff will assess AEs/conmeds of the subject. A physical exam may be performed at site investigator discretion.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions for the samples described below.

8.1 Tissue

8.1.1 Archival Tissue

Archival tumor tissue is required if available and will be identified at screening for correlative studies to evaluate and explore potential biomarkers in gastroesophageal adenocarcinoma, including DNA and RNA somatic mutation sequencing. Germline mutations will not be studied. If archival tissue is not available, the subject may still be eligible for the study provided they meet all other eligibility criteria.

8.1.2 Samples obtained during standard of care biopsy

Tissue samples remaining after routine standard of care procedures will be requested for correlative studies. Subject consent will be obtained.

8.2 Peripheral Blood Samples

Samples will be collected at Cycle 1 Day 1 visit, at the time of first restaging (prior to Cycle 6) and at the safety visit. Correlative analysis will include: ctDNA analysis and PBMCs for flow cytometry..

8.3 Stool Collection for Microbiome Analysis

Stool for microbiome analysis will be collected after registration to the study and prior to the start of treatment on C1D1.

8.4 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified cancer related research. Hoosier Cancer Research Network will manage the banked samples. Samples will be retained for 15 years.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1, at the time of first restaging (prior to Cycle 6) and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 at the time of first restaging (prior to Cycle 6) and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

8.5 Storage of Biospecimens

Any specimens remaining (leftover) once protocol described biospecimen-based studies are complete will be stored for future unspecified cancer related research for 15 years. Permission to retain the specimens will be obtained from subjects through informed consent.

8.6 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

For the purposes of this study, patients should be re-evaluated for response per the study calendar. Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1) (see Eisenhauer EA et al. *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Can, 2009.45:p.228-247) and the iRECIST criteria. See Seymour, L. et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3): e143-3152.

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

9.3 Target Lesions

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

largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

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

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) **NOTE:** If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.7 Definitions for Response Evaluation – RECIST 1.1

9.7.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

9.7.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.7.3 iRECIST
See Appendix C for details regarding iRECIST.

10. DRUG INFORMATION

10.1 mFOLFOX6
mFOLFOX6 is a chemotherapy regimen that includes leucovorin calcium (calcium folinate), 5-fluorouracil, and oxaliplatin. These drugs are commercially available and will be dispensed as such for this study. For more information on these agents, refer to the FDA approved package inserts.

10.1.1 Oxaliplatin
Oxaliplatin is a platinum alkylating agent, which contains platinum complexed to oxalate and diaminocyclohexane (DACH) complex. Platinum complexes are formed intracellularly and inhibit DNA synthesis through covalent binding of DNA molecules to form intrastrand and interstrand DNA cross-links. Oxaliplatin differs molecularly, from other platinums (cisplatin and carboplatin), by its bulky DACH carrier ligand that most likely accounts for both its efficacy and lack of cross-resistance with other platinum compounds. Cytotoxicity is cell-cycle nonspecific. Oxaliplatin is a radiationsensitizing agent.

*Oxaliplatin is incompatible with 0.9% NaCl. *Oxaliplatin is incompatible in solution with alkaline medications or media and must not be mixed with these. *Storage and handling materials containing aluminum parts that may come in contact with oxaliplatin should not be used for preparation or mixing of the drug, as aluminum can degrade platinum compounds.

1) The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution.

2) After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2º to 8°C (36º to 46° F)]. Do not freeze the concentrated solution.

3) The solution must be further diluted in an infusion solution of 250-500 mL of D5W. A final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions. Concentration must be between 0.2 to 0.7 mg/mL.

4) After final dilution with D5W, the shelf life is 6 hours at room temperature [20º to 25°C (68º to 77°F)] or up to 24 hours under refrigeration [2º to 8°C (36º to 46°F)].

5) Store under normal lighting conditions at 20°-25°C (68°-77°F); excursions permitted to 15-30°C (59- 86°F)]. Do not freeze.

10.1.2 Leucovorin

Leucovorin calcium (folinic acid) is a reduced form of folic acid. It is usually used 24 hours after methotrexate to selectively "rescue" normal cells from the adverse effects of methotrexate caused by inhibition of production of reduced folates. It is not used simultaneously with methotrexate, as it might then nullify the therapeutic effect of the methotrexate. Leucovorin has also been used to enhance the activity of fluorouracil by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of thymidylate. Leucovorin is available in D and L stereoisomers; the L stereoisomer is the active moiety.

* Each 50, 100, and 200 mg vial of Leucovorin when reconstituted with 5, 10, and 20 mL, respectively, of sterile diluent yields a leucovorin concentration of 10 mg per mL. Each 350 mg vial of Leucovorin when reconstituted with 17.5 mL of sterile diluent yields a leucovorin concentration of 20 mg per mL. *Leucovorin should not be mixed in the same infusion as fluorouracil as a precipitate may form.

1) Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, use immediately and discard any unused portion. Because of the benzyl alcohol contained in Bacteriostatic Water for Injection, when doses greater than 10 mg/m2 are administered, Leucovorin should be reconstituted with Sterile Water for Injection, and used immediately.

2) Dilute leucovorin in 50-1000 mL D5W or NS for infusion. Lecovorin may be mixed in 50mL NS or D5W minibag (doses up to 500mg) or 100mL minibag (doses >500mg) or in 100mL fluid in graduated administration set (D5W, NS or 2/3-1/3). Parenteral admixture is stable for 24 hours stored at room temperature (25°C) and for 4 days when stored under refrigeration (4°C).

3) Lyophilized powder vials should be stored at 20° to 25°C (68° to 77° F). Solution for injection should be stored in refrigerator 2° to 8°C (36° to 46°F). Protect from light. Retain in carton until time of use.

10.1.3 5 Fluorouracil

Fluorouracil was developed based on the observation that tumor cells utilized the base pair uracil for DNA synthesis more efficiently than did normal cells of the intestinal mucosa. It is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase).

*1 vial of Fluorouracil Injection contains: 500 mg fluorouracil in 10 ml solution (50 mg/ml); 1000 mg fluorouracil in 20 ml solution (50 mg/ml); 2500 mg fluorouracil in 50 ml solution (50 mg/ml); 5000 mg fluorouracil in 100 ml solution (50 mg/ml)

1) Fluorouracil may be mixed in a 50 mL minibag of NS or D5W, yielding a clear, colorless to light yellow solution. Solutions of fluorouracil are expected to be stable in solution 7 days at 37 °C, several weeks at 25 °C, and at least 4 months at 0-4 °C.

2) Store 5-fluorouracil in airtight containers protected from light.

10.1.4 Adverse Events

- Neuropathy
- Nausea
- Vomiting
- Increased liver function testing
- Diarrhea
- Fatigue
- Mucositis
- Abdominal pain
- Myelosuppression
- Infection
- bleeding
- Rash, hand-foot syndrome
- Pharyngolaryngeal dysesthesia

10.2 Trastuzumab

Trastuzumab is commercially available and will be dispensed as such for this study. Please refer to the latest version of the prescribing information for additional information. The biosimilar for trastuzumab may be used. Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Please refer to the latest version of the prescribing information for additional details for the biosimilar if used.

Trastuzumab is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

10.2.1 Supplier/How Supplied

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for Injection, for intravenous administration.

420 mg Multiple-dose vial

Trastuzumab for Injection 420 mg/vial is supplied in a multiple-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial of trastuzumab and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

150 mg Single-dose vial

Trastuzumab for Injection 150 mg/vial is supplied in a single-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial of trastuzumab.

10.2.2 Preparation for administration

420 mg Multiple-dose vial

Reconstitution

Reconstitute each 420 mg vial of trastuzumab with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab that delivers 20 mL (420 mg trastuzumab). In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of trastuzumab. The stream of diluent should be directed into the lyophilized cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Store reconstituted trastuzumab in the refrigerator at 2°C to 8°C (36°F to 46°F); discard unused Trastuzumab after 28 days. If Trastuzumab is reconstituted with SWFI without preservative, use immediately and discard any unused portion. **Do not freeze.**

Dilution

- Determine the dose (mg) of Trastuzumab *[see Dosage and Administration (2.2)]*. Calculate the volume of the 21 mg/mL reconstituted Trastuzumab solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.

- The solution of Trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. **Do not freeze.**

150 mg Single-dose vial
Reconstitution
Reconstitute each 150 mg vial of Trastuzumab with 7.4 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab).
Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized 150 mg Trastuzumab, directing the diluent stream into the lyophilized cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Use the Trastuzumab solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted Trastuzumab solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any unused Trastuzumab after 24 hours. **Do not freeze.**

Dilution

- Determine the dose (mg) of Trastuzumab *[see Dosage and Administration (2.1)]*.
- Calculate the volume of the 21 mg/mL reconstituted Trastuzumab solution needed.
- Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.
- The solution of Trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. **Do not freeze**.

10.2.3 Storage
Store Trastuzumab vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.

10.2.4 Adverse Events
Most common adverse reactions (≥ 10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation,

nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the Trastuzumab containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia. Less common adverse events that can be serious include embryo-fetal toxicity, pulmonary toxicity, cardiac toxicity, infusion reaction and exacerbation of chemotherapy-induced neutropenia. Please see prescribing information for full details regarding adverse events.

10.3 Avelumab

EMD Serono will supply avelumab for this study. Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody of the IgG1 isotype that specifically binds to the PD-L1 cell-surface molecule and blocks the interaction between PD-L1 and its receptors, programmed death 1 (PD-1) and B7-1.

10.3.1 Supplier/How Supplied

Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentration of 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween20). For avelumab drug product, only excipients that conform to the current Ph. Eur. and/or the current USP are used.

10.3.2 Preparation

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately. If not used immediately, it can be considered that the diluted product is sufficiently stable from a microbiological perspective for up to 8 hours when stored at ambient room temperature or up to 24 hours at 2°C to 8°C. The in-use storage times and conditions prior to administration are the responsibility of the user.

10.3.3 Storage and Stability

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with avelumab. Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

10.3.4 Handling and Disposal

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

10.3.5 Dispensing

Avelumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Avelumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.3.6 Adverse Events

Please see the Investigator's Brochure for complete details regarding adverse events. Common side effects include:

- Fatigue
- Peripheral edema
- Musculoskeletal pain (back pain, neck pain, pain in extremities)
- Diarrhea
- Nausea
- Infusion-related reactions (chills, fever, back pain, hypersensitivity reactions and low blood pressure,
- Rash and skin redness
- Decreased appetite

Immune mediated adverse events include: colitis, skin reaction, pulmonitis, liver dysfunction, renal failure, myocarditis, endocrine abnormalities and infusion reaction.

11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5.0 will be utilized for AE assessment. A copy of the CTCAE v5.0 can be downloaded from the CTEP website at http://ctep.cancer.gov.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of

central line) should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Other Reportable Events

These events are considered important medical events and should be reported as SAEs

- 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)

11.1.4 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.5 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until **30 days** after discontinuation of study drug(s) and/or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until **90 days** after discontinuation of study drug(s) and/or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event. The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to EMD Serono

HCRN will report all SAEs to EMD Serono as stipulated by company **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to EMD Serono as it is received from site.

Contact information for submission of reportable events to EMD Serono: Fax: +49 6151 72 6914 OR E-mail: icsr_CT_GPS@merckgroup.com Specify: PROTOCOL Number, SUBJECT Number, SITE Number/PI Name, and SAE/ONSET DATE.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the EMD Serono's parent IND at the time of submission. Additionally, HCRN will submit a copy of these documents to EMD Serono at the time of submission to FDA.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, HCRN will submit a copy of these reports to EMD Serono at the time of submission to FDA.

11.5 IND Safety Reports Unrelated to this Trial

IND Safety Reports unrelated to this trial will not be provided to HCRN. If there is an urgent safety issue related to Avelumab the sponsor-investigators will be informed immediately. HCRN will forward any urgent safety updates to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). Any urgent safety update will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these urgent safety updates to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

12.1 Study Design

The initial intent of this study was to be a prospective, open-label, single arm, multi-center phase 2 clinical trial of avelumab + trastuzumab + mFOLFOX6 in first-line, metastatic, HER2-amplified gastric and esophageal adenocarcinomas. Accrual will halt after enrollment of 18 subjects (completion of Stage I). This decision is not due to safety issues. Subjects currently on treatment will continue until criteria as defined in Section 6.7 is met.

The primary objective of this study is to estimate the best objective response rate (CR or PR, ORR) in these patients within 24 weeks by RECIST 1.1 criteria. Secondary objectives include; estimating PFS by both RECIST 1.1 and iRECIST criteria, estimating OS, estimating the disease control rate (DCR) at 24 weeks by RECIST 1.1 and iRECIST, and characterizing the safety issues associated with this regimen. Exploratory objectives involve investigating various biomarkers and peripheral blood and tumor assays.

12.2 Sample Size and Accrual

The objective response rate of treatment with mFOLFOX6 + trastuzumab alone (per ToGA) is approximately 47%. The objective response rate of the treatment regimen which contains the addition of avelumab to mFOLFOX6 + trastuzumab is expected to be 65%. A Simon two-stage optimal design will be used, with alpha = 0.05 and 80% power, and with the null and alternative hypothesis response rates of 47% and 65%, respectively.

In the first stage, 18 evaluable patients will be enrolled and treated. If only 9 (or less) of these 18 patients are responders during this first stage, the trial will be suspended for futility. Enrollment will halt after this first stage.

The intent was that if 10 (or more) responses are observed, then another 39 patients would be enrolled and treated in the second stage, for a total of 57 evaluable patients. If only 32 patients (or less) of the final total of 57 evaluable patients responded to this treatment regimen, then the regimen would not be considered of clinical interest. If 33 or more responses were observed among the 57 evaluable patients, then the treatment regimen would be considered of clinical interest and would therefore justify further development. Assuming a possible 10% consent and not treat or loss to follow-up rate, a total of 63 patients were planned for accrual. Accrual was expected to take approximately 22 months.

12.3 Toxicity Monitoring

Toxicity will be assessed using NCI CTCAE version 5. Patients will be monitored for excessive toxicity over the duration of the study. A toxicity rate due to the study regimen greater than 35% would be considered unacceptable (with a desired probability of early stopping of 0.05). Toxicity events that will be monitored are defined as those that call for permanent discontinuation of avelumab, as defined in Section 6.3 or any grade 3-4 treatment-related adverse events that require holding all treatments for more than 14 days.

Pocock-type boundaries will be utilized as described in Ivanova, A., et al. Biometrics. 2005; 61(2):540-5. If a toxicity boundary is reached, accrual for the study will be suspended and the

Data Safety Monitoring Board (DSMB) will be alerted. The DSMB (in consultation with the sponsor-investigator) will evaluate the toxicity events to help determine whether or not to terminate the study.

Accrual to the trial is to be suspended if the number of protocol defined toxic events as defined above is equal to or larger than boundary in the table below.

Number of Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary	-	-	-	-	5	6	6	7	7	8	9	9	10	10	11	11	12	12	12	13
Number of Patients	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary	13	14	14	15	15	16	16	17	17	18	18	18	19	19	20	20	21	21	22	22
Number of Patients	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary	22	23	23	24	24	25	25	25	26	26	27	27	28	28	28	29	29	30	30	31

12.4 Assessment of Safety

All subjects who have received at least one dose of study treatment will be evaluable for assessment of safety. CTCAE v5 will be used for assessment of safety.

12.5 Assessment of Efficacy

All subjects who have received at least one cycle of study treatment and have had at least one post baseline disease assessment or die of any cause before the first post baseline disease assessment will be evaluable for assessment of efficacy. Only subjects who have a CR or PR by RECIST 1.1 will be considered responders. Consequently, for all subjects who discontinue study treatment before documentation of progression, every effort should be made to document the objective progression even after discontinuation of treatment.

12.6 Definitions

- Best Objective Response Rate (bORR): The best objective response rate will be defined as the total number of patients whose best response by 24 weeks are either a CR or PR divided by the number of response evaluable patients
- Progression Free Survival (PFS): A patient's progression-free survival (PFS) will be defined as the time from the start date of treatment to the date of documented progression or death. Any patient who has received study treatment but has neither progressed nor died will be censored on the date the patient was known to be alive and progression free.
- Overall Survival (OS): A patient's survival time will be defined as the time from start of treatment to the date of his or her death. If the patient has not died, survival will be censored on last date the patient was known to be alive.
- Disease Control Rate (DCR): The disease control rate used to help determine clinical benefit will be defined as the total number of patients whose responses are either a CR, PR, or SD divided by the number of response evaluable patients. Patients will need to be at least a SD for at 24 weeks to be considered to have received clinical benefit from the treatment regimen

12.7 Data Analyses Plans

bORR and DCR will be calculated and reported with their corresponding 95% confidence intervals. PFS and OS estimates will be calculated using the Kaplan-Meier method. The primary analysis will apply to the total number of efficacy-evaluable patients. Toxicity and safety information will be reported in a descriptive manner in the form of frequency tables. Adverse events will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Hypothesis generating exploratory analyses will be performed when appropriate sample size considerations allow. Baseline tumor studies may include PD-L1 expression, degree of HER2 amplification, sequencing of low-diversity B and T cell receptors, and RNASeq to include deconvolution of immune cell infiltrates. Changes in circulating markers of immune activation and circulating tumor DNA levels will be evaluated using peripheral blood samples collected at baseline, at first restaging, and at the end of treatment.

13 TRIAL MANAGEMENT

13.1 Data Safety Monitoring Board

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB is chaired by an independent medical oncologist external to this trial. The DSMB will meet quarterly during the active treatment and safety follow-up portion of the trial to review information. The DSMB will provide a recommendation to the sponsor-investigator after all information is reviewed.
The DSMB review will include but is not limited to:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

13.2 Data Quality Oversight Activities by HCRN

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause audits may be performed as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by EMD Serono or its designee as well as inspection by appropriate regulatory agencies.

13.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, EMD Serono, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

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

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16 APPENDICES

APPENDIX A: ECOG Performance Status Scale

Score	Definition	Karnofsky Equivalent
0	Asymptomatic	100
1	Symptomatic, fully ambulatory	80 – 90
2	Symptomatic, in bed less than 50% of day	60 – 70
3	Symptomatic, in bed more than 50% of day, but not bedridden	40 – 50
4	Bedridden	20 – 30

APPENDIX B: Cockcroft-Gault Formula

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

APPENDIX C: Immune-RECIST Criteria

Table 1: Comparison of RECIST 1.1 and iRECIST		
	RECIST 1.1	**iRECIST**
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomized trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD
"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumors. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.		

Table 2: Assignment of timepoint response using iRECIST		
	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified
Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumors.		

Reference: Seymour, L. et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3): e143-3152.

17 REFERENCES

1. Nagini, S., *Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention.* World J Gastrointest Oncol, 2012. **4**(7): p. 156-69.
2. Glimelius, B., et al., *Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer.* Ann Oncol, 1997. **8**(2): p. 163-8.
3. Pyrhonen, S., et al., *Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer.* Br J Cancer, 1995. **71**(3): p. 587-91.
4. *Comprehensive molecular characterization of gastric adenocarcinoma.* Nature, 2014. **513**(7517): p. 202-9.
5. Dulak, A.M., et al., *Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity.* Nat Genet, 2013. **45**(5): p. 478-86.
6. Yoon, H.H., et al., *HER-2/neu gene amplification in relation to expression of HER2 and HER3 proteins in patients with esophageal adenocarcinoma.* Cancer, 2014. **120**(3): p. 415-24.
7. Bang, Y.J., et al., *Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial.* Lancet, 2010. **376**(9742): p. 687-97.
8. *HERCEPTIN® (trastuzumab): Highlights of prescribing information*. 2010; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf.
9. Cancer Genome Atlas Research, N., et al., *Integrated genomic characterization of oesophageal carcinoma.* Nature, 2017. **541**(7636): p. 169-175.
10. Cancer Genome Atlas Research, N., *Comprehensive molecular characterization of gastric adenocarcinoma.* Nature, 2014. **513**(7517): p. 202-9.
11. Stagg, J., et al., *Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy.* Proc Natl Acad Sci U S A, 2011. **108**(17): p. 7142-7.
12. Varadan, V., et al., *Immune Signatures Following Single Dose Trastuzumab Predict Pathologic Response to Preoperative Trastuzumab and Chemotherapy in HER2-Positive Early Breast Cancer.* Clin Cancer Res, 2016.
13. Milano, F., et al., *Trastuzumab mediated T-cell response against HER-2/neu overexpressing esophageal adenocarcinoma depends on intact antigen processing machinery.* PLoS One, 2010. **5**(8): p. e12424.
14. Shebzukhov, Y.V., et al., *Humoral immune response to thymidylate synthase in colon cancer patients after 5-FU chemotherapy.* Immunol Lett, 2005. **100**(1): p. 88-93.
15. Bracci, L., et al., *Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer.* Cell Death Differ, 2014. **21**(1): p. 15-25.
16. Correale, P., et al., *Dendritic cell-mediated cross-presentation of antigens derived from colon carcinoma cells exposed to a highly cytotoxic multidrug regimen with gemcitabine,*

oxaliplatin, 5-fluorouracil, and leucovorin, elicits a powerful human antigen-specific CTL response with antitumor activity in vitro. J Immunol, 2005. **175**(2): p. 820-8.
17. Boger, C., et al., *PD-L1 is an independent prognostic predictor in gastric cancer of Western patients.* Oncotarget, 2016. **7**(17): p. 24269-83.
18. Oki, E., et al., *Protein Expression of Programmed Death 1 Ligand 1 and HER2 in Gastric Carcinoma.* Oncology, 2017.
19. Satoh, T., et al., *Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study.* J Clin Oncol, 2014. **32**(19): p. 2039-49.
20. Kang, Y.-K., et al., *A randomized, open-label, multicenter, adaptive phase 2/3 study of trastuzumab emtansine (T-DM1) versus a taxane (TAX) in patients (pts) with previously treated HER2-positive locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (LA/MGC/GEJC).* J Clin Oncol, 2016. **34**: p. suppl 4S; abstr 5.
21. Janjigian, Y.Y., et al., *Loss of human epidermal growth factor receptor 2 (HER2) expression in HER2-overexpressing esophagogastric (EG) tumors treated with trastuzumab.* J Clin Oncol, 2016. **33**: p. suppl 3; abstr 63.
22. Ruschoff, J., et al., *HER2 testing in gastric cancer: a practical approach.* Mod Pathol, 2012. **25**(5): p. 637-50.
23. Hu-Lieskovan, S., et al., *Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF(V600E) melanoma.* Sci Transl Med, 2015. **7**(279): p. 279ra41.
24. Hu-Lieskovan, S., et al., *Combining targeted therapy with immunotherapy in BRAF-mutant melanoma: promise and challenges.* J Clin Oncol, 2014. **32**(21): p. 2248-54.
25. Kang, Y.-K., et al., *Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial.* J Clin Oncol, 2017. **35**: p. suppl 4S; abstract 2.
26. Kang, Y.K., et al., *Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2017. **390**(10111): p. 2461-2471.
27. Janjigian, Y.Y., et al., *Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study.* . J Clin Oncol, 2017. **35**(no.15_suppl): p. 4014.
28. Fuchs, C.S., et al., *KEYNOTE-059 cohort 1: Efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer.* J Clin Oncol, 2017. **35**(no. 15_suppl): p. 4003.
29. Loi, S., et al. *Phase Ib/II study evaluating safety and efficacy of pembrolizumab and trastuzumab in patients with trastuzumab-resistant HER2-positive metastatic breast cancer: Results from the PANACEA (IBCSG 45-13/BIG 4-13/KEYNOTE-014) study*. in *San Antonio Breast Cancer Symposium*. 2017.