TITLE:	**Phase II trial of perioperative PD-L1 inhibition with Avelumab and Docetaxel, Cisplatin, and 5-Fluorouracil for Resectable Locally Advanced Esophago-Gastric Adenocarcinoma**
BRIEF TITLE:	mDCF + Avelumab in resectable EGA
PROTOCOL N°:	MS100070_0073
PRINCIPAL INVESTIGATOR:	Thierry Alcindor, MD, MSc, FRCP(C)
SPONSOR:	McGill University Health Centre
VERSION N°:	2.0
DATE:	18 July 2019
TEST PRODUCT:	Avelumab (Anti-PD-L1 mAb)
FUNDING:	EMD Serono

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LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CT	Computerized tomography
DCF	Docetaxel, cisplatin, 5-fluorouracil regimen
DFS	Disease-free survival
EGA	Esophago-gastric adenocarcinoma
FDG	Fludeoxyglucose (^{18}F)
GCP	Good Clinical Practice
irAE	Immune-related adverse event
LFT	Liver function test
LLN	Lower limit of normal
mDCF	Modified docetaxel, cisplatin, 5-fluorouracil regimen
MRI	Magnetic resonance imaging
MUHC	McGill University Health Centre
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NSAID	Nonsteroidal anti-inflammatory drugs
OS	Overall survival
pCR	Pathologic complete response
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
SAE	Serious adverse event
T4	Free thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: *Ethical Principles for Medical Research Involving Human Participants*, as well as applicable regulatory and institutional requirements.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training).

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____
Thierry Alcindor, MD, MSc, FRCP(C)

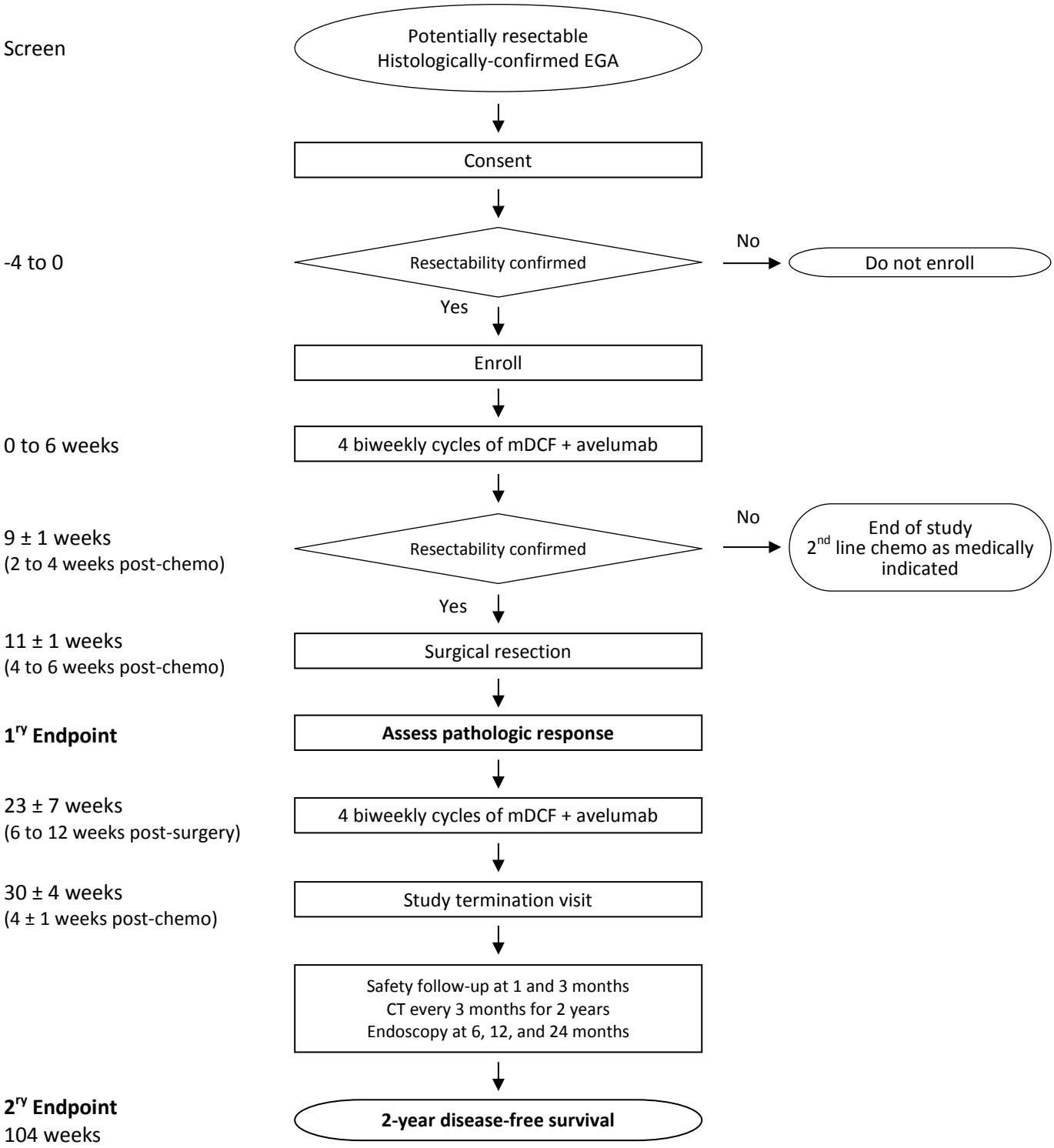
Date: _____

PROTOCOL SUMMARY

Title:	Phase II trial of perioperative PD-L1 inhibition with Avelumab and Docetaxel, Cisplatin, and 5-Fluorouracil for Resectable Locally Advanced Esophago-Gastric Adenocarcinoma (EGA)
Brief title:	mDCF + Avelumab in resectable EGA
Design:	This is a single-center, single-arm, open-label, Simon 2-stage, phase II trial in up to 55 patients with a potentially resectable, histologically-proven, adenocarcinoma or poorly differentiated carcinoma of the stomach, esophagogastric junction (EGJ), or lower third of the esophagus. Patients will receive neoadjuvant therapy consisting of 4 cycles of avelumab added to the modified chemotherapy regimen of docetaxel, cisplatin, 5-fluorouracil. Following surgery, pathologic response will be assessed. Patients will then receive adjuvant therapy consisting of 4 cycles of mDCF + avelumab. Patients will be followed to assess two-year disease-free survival rates.
Objectives:	The primary objective of this study is to assess the effect on pathologic complete response rate (pCR) of adding avelumab to an mDCF regimen. The secondary objectives of this study are to: • determine the safety of adding avelumab to an mDCF regimen • assess the effect on two-year disease-free survival, of adding avelumab to an mDCF regimen.
Endpoint	Primary Endpoint: pathologic complete response (pCR) Secondary Endpoints: two-year disease-free survival, and incidence of grade 3 or 4 avelumab-related adverse events.
Population:	• Up to 55 male or female patients older than 18 years of age; • Potentially resectable, histologically-confirmed adenocarcinoma or poorly differentiated carcinoma of the stomach, esophagogastric junction (EGJ), or lower third of the esophagus • Stage IB (T1N1 only), II, IIIA, IIIB • Life expectancy greater than 3 months • ECOG performance status of 0-1
Phase:	2
Study site(s)	McGill University Health Centre Medical Oncology Cedars Cancer Centre

	1001 Décarie Boulevard Montreal, Quebec H4A 3J1
Study drug:	Two courses of four cycles of biweekly intravenous infusion of Avelumab 800 mg fixed dose. Avelumab is a fully human antibody of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1. Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (IV) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab.
Study Duration:	Three years.
Participant Duration:	The final visit takes place up to 30 ± 4 weeks after the first cycle of treatment. There will be one telephone follow-up or visit 90 days later to assess any delayed immune reactions. Patients will be followed for up to two years following the last dose of avelumab.

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Principal Investigator:

Thierry Alcindor, MD
McGill University Health Centre
Medical Oncology
Cedars Cancer Centre
1001 Décarie Boulevard
Montreal, Quebec H4A 3J1
Telephone: (514) 934-1934 ext 43118
E-mail: thierry.alcindor@mcgill.ca

Co-investigators:

Dr. Lorenzo Ferri
Thoracic Surgery/Surgical Oncology
lorenzo.ferri@mcgill.ca

Dr. Carmen Mueller
Thoracic Surgery/Surgical Oncology
carmen.mueller@mcgill.ca

Dr. Marie Vanhuyse
Medical Oncology
marie.vanhuyse@mcgill.ca

Dr. Jamil Asselah
Medical Oncology
jamil.asselah@mcgill.ca

Dr. Victoria Marcus
Pathology
victoria.marcus@muhc.mcgill.ca

Monitoring:

The Research Institute of the
McGill University Health Centre
2155 Guy Street, 5th Floor
Montreal, Que H3H 2R9

Statistical analysis:

The Research Institute of the
McGill University Health Centre

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Surgery remains the primary curative treatment modality for patients with gastric and esophago-gastric junction adenocarcinoma (EGJ adenocarcinoma) [1,2]. In the United States and Europe, the 5-year survival is 30-40% and most patients die from locoregional and distant metastases [3].

The five-year survival rate for patients with completely resected early-stage gastric cancer is approximately 75 per cent, while it is 30 per cent or less for patients who have extensive lymph node involvement [3-5]. The addition of perioperative chemotherapy has significantly improved outcomes [6]. This approach utilizes chemotherapy before and after surgery with the aim of shrinking and downstaging the tumour, and to eradicate potential micrometastatic disease. The target patients with localized gastric cancer are typically at increased risk of developing clinically significant metastatic disease. This high-risk group includes patients with T3/T4 tumours, visible perigastric nodes, linitis plastica, and positive peritoneal cytology in the absence of demonstrative peritoneal disease.

2.2 RATIONALE

Several active chemotherapy regimens have been identified, including cisplatin/5-fluorouracil (CF), epirubicin/cisplatin/5-fluorouracil (ECF), docetaxel/cisplatin/5-fluorouracil (DCF) [5,7-19]. Perioperative CF and ECF have both been evaluated in randomized controlled trials, and shown a survival advantage when added to surgery in comparison to surgery alone (5-year disease-free survival [DFS] and overall survival [OS] of 30-35% and 35-40%, respectively) [6,20]. Our group has investigated DCF in a single-arm phase II trial and found promising results (5-year DFS and OS of 60% and 53%, respectively) with the addition of a taxane [21]. Regardless, there remains room for improvement in terms of efficacy and tolerability of the regimens used, given the persistent high rate of systemic recurrence. Chemotherapy-induced tumor regression appears to correlate to a certain extent with improved progression-free survival (PFS), especially when pathologic complete response (pCR) is observed [22]. Efforts to improve pCR rate are thus a rational strategy.

The commonly used cisplatin-based perioperative chemotherapy regimens only yield a 5-10% pCR rate [20]. Given the encouraging activity of single-agent anti-PD-1/PD-L1 antibody therapy, we are hypothesizing an additive or a synergistic effect of avelumab, an anti-PD-L1 antibody, with chemotherapy. A modified version of DCF, mDCF, given every 2 weeks, will be used for this trial, having shown equivalent activity and lesser toxicity in comparison to standard DCF, which is administered every 3 weeks [7,10,23]. The biweekly schedule also matches that of avelumab. The mDCF/avelumab combination will be given intravenously every 2 weeks, for 4 cycles before and after surgery.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 Known Potential Risks

2.3.1.1 Cisplatin

Cisplatin is an alkylating antineoplastic agent. Cisplatin is highly protein bound with distribution to kidneys, liver, and intestines[24]. Only 25% to 45% of the administered dose is excreted in the urine. The major dose-limiting toxicity of cisplatin is cumulative nephrotoxicity which can occur in 28-36 % of patients[24]. This side-effect can be minimized or prevented by selection of patients with adequate renal function (see inclusion/exclusion criteria), and IV hydration with diuresis.

Metabolic abnormalities such as acidosis, hypomagnesemia, hypophosphatemia, hyponatremia or hypokalemia may be present and require close follow-up on blood work [24]. Hypomagnesemia may persist for over a year following treatment. Various degrees of nausea and anorexia may persist for up to 1 week, even with well-controlled acute nausea and vomiting. The use of prophylactic and continuing antiemetic medication is standard and will be provided to all patients. Neurotoxicity consists of peripheral neuropathy, which is sensory in nature but can also include motor effects, reduced deep-tendon reflexes and loss of proprioception [24]. Symptoms usually occur after prolonged therapy (4-7 months) and may be irreversible. Cisplatin should be discontinued if neuropathic symptoms interfere with activities of daily living (grade 3) [24]. Ototoxicities consist of audiogram abnormalities in 24% of patients. Auditory impairment usually results in impairment of acuity in the high frequency range, but may affect the normal hearing range in 6% of cases [24]. Ototoxicity is cumulative, dose related and irreversible [24]. Patients will be screened by history for hearing impairment with pre-enrolment audiograms if necessary.

Hypersensitivity reactions including anaphylaxis are very rare and should be treated with antihistamines and hydrocortisone (cisplatin may be discontinued depending on the severity of the reaction). Myelosuppression with neutropenia can occur, and there will be primary prophylaxis in this study with filgastrim or pegfilgastrim. Anemia can result from prolonged cisplatin therapy and should be corrected at the discretion of the treating physician.

Cisplatin is commercially available.

2.3.1.2 Docetaxel

Docetaxel, a semisynthetic taxoid produced from the needles of the European yew is an antineoplastic drug belonging to the same class as paclitaxel [25]. The drug acts by disrupting the microtubular network in cells that is essential for cell division. Docetaxel is metabolized in the liver. Hepatic impairment reduces drug clearance (see inclusion /exclusion criteria).

The major dose-limiting adverse effect of docetaxel is myelosuppression [25]. Neutropenia is reversible and not cumulative. Febrile neutropenia can occur. Prophylaxis with filgrastim or pegfilgrastim has already been mentioned. Anemia can result from prolonged therapy and management guidelines are similar to cisplatin.

Severe hypersensitivity reactions characterized by hypotension, bronchospasm or generalized rash/erythema could occur within a few minutes following the initiation of infusion of docetaxel and occurs in 4% of patients [25]. All patients will be pre-medicated with dexamethasone to prevent severe reactions. Treatment for these sensitivity reactions (depending on the severity) include immediate interruption of the infusion, IV administration of diphenhydramine with or without dexamethasone and/or epinephrine as needed. Pre-medication with an oral or IV antihistamine prior to the next cycle of docetaxel or discontinuation of docetaxel therapy can be decided according to investigator judgment of the severity. Asthenia associated with docetaxel is common [25]. Symptoms of fatigue and weakness may persist for a few days to several weeks following administration.

Docetaxel-induced fluid retention is usually completely reversible with resolution after approximately 4 months from the last infusion. Peripheral edema can be treated with standard measures (e.g. sodium restriction, diuretics). Severe fluid retention occurs in 7 % of patients, and is characterized by poorly tolerated peripheral edema, generalized edema, pleural effusions requiring urgent drainage, dyspnea at rest, cardiac tamponade, and/or pronounced abdominal distention caused by ascites [25]. For these cases the drug should be discontinued. Cutaneous reactions are dose-dependent and cumulative, characterized by localized eruptions mainly on feet and hands (palmar-planter dysesthesia), but may occur elsewhere and be associated with pruritus [25]. Nail disorders, including altered pigmentation, occasional onycholysis and pain may occur. Musculoskeletal manifestations usually are transient, occurring within a few days after docetaxel administration and lasting about 4 days. Mild analgesics (e.g. acetaminophen) are effective.

Docetaxel can cause a dose-related predominantly sensory neuropathy characterized by paresthesia or dysesthesia with numbness and tingling in a stocking-and-glove distribution [25]. Severe symptoms (grade 3) are rare but require dose modifications [25]. Sensory manifestations usually improve or resolve following discontinuation of docetaxel.

Docetaxel is commercially available

2.3.1.3 Fluorouracil (5-FU)

5-FU is a fluorinated pyrimidine that is metabolized intracellularly to its active form which inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. The drug is eliminated predominantly by the liver (see inclusion/exclusion criteria). Following longer IV infusions as in this protocol, stomatitis and diarrhea occur commonly. Diarrhea may be profuse and cause significant dehydration. Aggressive treatment of diarrhea with hydration (intravenous if necessary) and antidiarrheals (loperamide, lomotil, octreotide) may be necessary.

Neutropenia is uncommon with protracted continuous infusion regimens as in this study, but will be prevented with growth factor support. Patients with deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD) are at risk of severe life threatening toxicity with fluorouracil. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency.

Palmar-plantar erythrodysesthesia or hand-foot syndrome has been noted with continuous infusion (23-82%). The syndrome begins with dysesthesias of the palms and soles that progress to pain and tenderness. Treatment with 50 or 150 mg of pyridoxine daily has been associated with reversal of the syndrome. The syndrome resolves with cessation of drug infusion.

5-FU is commercially available.

2.3.1.4 Surgery

Surgery remains the cornerstone of curative intent treatment of esophageal and gastric adenocarcinoma. The rate of morbidity after gastrectomy ranges between 15-40%, and include both medical (e.g. pneumonia) and surgical complications (anastomotic leak, pancreatic leak, intra-abdominal abscess) [1,6,26,27]. Complications after esophagectomy are typically higher, but overall mortality can be kept low (approximately 2%), if managed in high-volume centres such as the McGill University Health Centre. In a recently reported trial, no increase in morbidity or mortality was witnessed with the addition of chemotherapy prior to gastric resection [6]. Although initial studies revealed an increased rate of complication with D2 celiac lymph node dissection, it is felt to be due to inexperience with the complicated procedure and a steep learning curve, as more recent studies have failed to demonstrate a difference in complication rates between D1 and D2 lymphadenectomy [26-28]. Indeed, recent evidence demonstrates that extended lymphadenectomy (D2 dissection) can be performed safely by experienced surgeons, increases lymph node yield, is associated with improved long-term oncologic outcomes in lymph node positive patients, and thus should be the standard of care in patients with locally advanced esophageal and gastric cancer [27]. D2 dissection is recommended in this clinical trial.

2.3.1.5 Avelumab

For a complete discussion of the potential risks related to avelumab, consult the Investigator's Brochure, section 5.4.1 *Safety*.

Avelumab, an investigational drug, is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand for PD-1 (PD-L1). As such, it shares many of the side effects observed with other antibodies of the PD-1/PD-L1 axis. Safety data have been tabulated from studies of 1300 subjects treated in Phase I trials. The pooled data include subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck.

All AES

Overall, 1200 of 1300 patients (92.3%) reported at least one adverse event (AE). At least one AE was considered related to avelumab in 813 patients (62.5%). At least one related AE of grade 3 or more was reported in 124 patients (9.5%). (Table 1)

Table 1: Adverse Events

Adverse Event (MedDRA preferred term)	All AEs	Related AEs	Related AEs ≥ Grade 3
Fatigue	356 (27.4%)	212 (16.3%)	8 (0.6%)
Nausea	276 (21.2%)	108 (8.3%)	
Infusion-related reaction	211 (16.2%)	209 (16.1%)	9 (0.7%)
Diarrhea	205 (15.8%)	79 (6.1%)	
Constipation	204 (15.7%)	26 (2.0%)	
Decreased appetite	194 (14.9%)	60 (4.6%)	3 (0.2%)
Vomiting	188 (14.5%)	46 (3.5%)	3 (0.2%)
Weight decreased	159 (12.2%)		
Abdominal pain	156 (12.0%)		
Anaemia	155 (11.9%)	30 (2.3%)	7 (0.5%)
Cough	152 (11.7%)		
Dyspnoea	148 (11.4%)		6 (0.5%)
Pyrexia	148 (11.4%)	72 (5.5%)	
Chills	137 (10.5%)	102 (7.8%)	
Arthralgia		53 (4.1%)	
Hypothyroidism		45 (3.5%)	
Influenza like illness		42 (3.2%)	
Pruritus		40 (3.1%)	
Myalgia		37 (2.8%)	
Rash		36 (2.8%)	
Headache		34 (2.6%)	
Asthenia		29 (2.2%)	3 (0.2%)
Aspartate aminotransferase increased		26 (2.0%)	5 (0.4%)
Gamma-glutamyltransferase increased			9 (0.7%)
Lipase increased			8 (0.6%)
Autoimmune hepatitis			4 (0.3%)
Pneumonitis			4 (0.3%)
Alanine aminotransferase increased			3 (0.2%)
Blood creatine phosphokinase increased			3 (0.2%)
Colitis			3 (0.2%)
Hypokalaemia			3 (0.2%)
Hypoxia			3 (0.2%)
Lymphocyte count decreased			3 (0.2%)
Myositis			3 (0.2%)
Transaminases increased			3 (0.2%)

Source: Avemulab Investigator's Brochure Version 6, Tables 15, 16, and 17

Serious AEs

Serious AEs (SAEs) were reported in 509 patients (39.2%); the SAE was considered related to avelumab in 71 patients (5.5%). (Table 2)

Non-serious AEs and SAEs resulted in permanent discontinuation of treatment in 175 patients (13.5%). Related non-serious AEs and SAEs resulted in permanent discontinuation of treatment in 79 patients (6.1%).

Table 2: SAEs, and AEs Leading to Discontinuation

Adverse Event (MedDRA preferred term)	All SAEs	Related SAEs	All discontinuation*
Dyspnoea	42 (3.2%)	5 (0.4%)	2 (0.2%)
Pneumonia	29 (2.2%)		
Pleural effusion	28 (2.2%)		
Abdominal pain	27 (2.1%)	2 (0.2%)	
Vomiting	19 (1.5%)	2 (0.2%)	
Small intestinal obstruction	17 (1.3%)		
Anaemia	16 (1.2%)		
Nausea	16 (1.2%)		
Pyrexia	15 (1.2%)	5 (0.4%)	
Respiratory failure	15 (1.2%)		
Asthenia	14 (1.1%)	2 (0.2%)	
Ascites	14 (1.1%)		
Sepsis	14 (1.1%)		
Disease progression	102 (7.8%)		
Infusion-related reaction		11 (0.8%)	25 (1.9%)
Pneumonitis		8 (0.6%)	
Autoimmune hepatitis		3 (0.2%)	2 (0.2%)
Blood creatine phosphokinase increased		2 (0.2%)	3 (0.2%)
Colitis		2 (0.2%)	2 (0.2%)
Adrenal insufficiency		2 (0.2%)	
Diarrhoea		2 (0.2%)	
Hyponatraemia		2 (0.2%)	
Non-cardiac chest pain		2 (0.2%)	
Gamma-glutamyltransferase increased			5 (0.4%)
Aspartate aminotransferase increased			3 (0.2%)
Lipase increased			3 (0.2%)
Alanine aminotransferase increased			2 (0.2%)
Arthralgia			2 (0.2%)
Fatigue			2 (0.2%)
Myositis			2 (0.2%)
MedDRA PT not coded			2 (0.2%)

Source: Avemulab Investigator's Brochure Version 6, Tables 20, 21, and 22
* Includes AEs and SAEs

Potential Immune-related AEs

Potential immune-related adverse events (irAE) were reported in 149 of 1300 subjects (11.5%); 99 of these were considered to be treatment-related (7.6%).

Hypothyroidism was the most frequent treatment-related potential irAE (Table 3).

Table 3: Immune-related AE

Adverse Event (MedDRA preferred term)	All irSAEs	Related irAEs
Hypothyroidism	56 (4.3)	45 (3.5%)
Pneumonitis	19 (1.5)	13 (1.0%)
Hyperthyroidism	15 (1.2)	7 (0.5%)
Dry eye	13 (1.0)	5 (0.4%)
Adrenal insufficiency	10 (0.8)	5 (0.4%)
Arthritis	9 (0.7)	
Thrombocytopenia	8 (0.6)	
Colitis	5 (0.4)	4 (0.3%)
Autoimmune hepatitis	4 (0.3)	4 (0.3%)
Radiation pneumonitis	4 (0.3)	≤ 2 (0.15%)
Encephalopathy	3 (0.2)	≤ 2 (0.15%)
Myositis	3 (0.2)	3 (0.2%)
Psoriasis	3 (0.2)	≤ 2 (0.15%)
Radiculopathy	3 (0.2)	≤ 2 (0.15%)
Thyroiditis	3 (0.2)	≤ 2 (0.15%)
Autoimmune thyroiditis	2 (0.2)	≤ 2 (0.15%)
Rheumatoid factor increased	2 (0.2)	≤ 2 (0.15%)

Source: Avemulab Investigator's Brochure Version 6, Table 23, and 5.4.1.1.2.6 *TEAEs of Special Interest*

The majority of potential irAEs were Grade 1 or Grade 2 events. Potential irAEs ≥ Grade 3 occurred in 29 (2.2%) subjects; 20 (1.5%) were considered treatment-related.

Twenty-eight subjects (2.2%) experienced serious all causality potential irAEs; 22 (1.7%) were considered treatment-related

Potential irAEs that led to treatment discontinuation occurred in 15 subjects (1.2%); all were deemed treatment-related.

Potential irAEs leading to death occurred in 3 (0.2%) subjects, which were all assessed as treatment-related events (pneumonitis [Grade 5]; radiation pneumonitis [Grade 5]; autoimmune hepatitis [not confirmed by liver biopsy/autopsy]). In addition, one subject died of suspected Grade 3 autoimmune hepatitis (not confirmed by liver biopsy/autopsy) with fatal outcome due to acute liver failure. Narratives for these cases are provided in the Investigator's Brochure Section 8.2.

Anti-Drug Antibody Response

Anti-drug antibody (ADA) data were available for 339 of 1300 subjects; it was positive in 10 (2.95%). Two subjects had symptoms on the day of the infusion consistent with a possible hypersensitivity reaction (chills, fever, nausea, and vomiting) and may be ADA related. No hypersensitivity reactions were observed in the remainder.

Infusion-related Reactions

At least one episode of infusion-related reaction was experienced by 215 of 1300 subjects (16.5%). Most of the events were Grade 1 (53 subjects, 4.1%) or Grade 2 (153 subjects, 11.8%) in intensity. Six patients had Grade 3 events (0.5%); three had a Grade 4 event (0.2%). No Grade 5 events were reported.

Most of the infusion-related reactions had an onset after the first (149 subjects, 11.5%) or second (48 subjects, 3.7%) avelumab infusion. The onset was after the third infusion in 12 subjects (0.9%) or fourth or later avelumab infusion in 6 subjects (0.5%).

Avelumab treatment was discontinued because of infusion-related reaction in 23 subjects (1.8%).

Deaths

As of the adverse event cut-off date, there had been 466 deaths (35.8%) among the 1300 subjects. A total of 142 deaths (10.9%) occurred within 30 days of last treatment. The majority of deaths were due to progressive disease (360 subjects; 27.7%).

The primary reason for death was assessed by the investigator as being due to an adverse event not related to treatment in 33 subjects (2.5%) and to an AE related to treatment in 5 subjects (0.4%). In addition to the four treatment-related deaths described above under *Potential immune-related AEs*, one death due to respiratory distress and sepsis was considered treatment-related. Two additional cases of death were reported and assessed as treatment-related, but the treatment related TEAEs were not considered as the primary reason of the death (fatal anoxic brain injury [not related] after cardiac arrest [related]; and acute respiratory failure with acute exacerbation of COPD). Narratives for these cases are provided in the Investigator's Brochure Section 8.2.

2.3.2 Known Potential Benefits

Because of the known role of programmed death ligand 1 (PD-L1) in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, the blockade of the PD-L1/programmed death 1 (PD-1) interaction presents a highly promising strategy for cancer immunotherapy [29,30]. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

As avelumab is in only in Phase II, no definitive statements can be made on known potential benefits. However, avelumab was evaluated in the Javelin Merkel 200 phase II trial in 88 patients with

chemotherapy-refractory merkel cell carcinoma [31]. Avelumab was found to have an objective response rate of 31.8% (9.1% complete response and 22.7% partial response) with 5 (5.8%) patients with grade 3 adverse events including 2 cases of lymphopenia, 1 case each of elevated creatine kinase, cholesterol and ALT [31]. There were no treatment-related grade 4 or 5 events [31]. Based on these findings, avelumab is under priority review by the US Food and Drug Administration for licensure.

Immune checkpoint blockade with inhibitors for PD-1 or PD-L1 have shown activity in advanced/metastatic gastric and gastroesophageal adenocarcinomas. Phase 1 data for avelumab in second-line advanced gastric and esophageal adenocarcinoma with 62 patients showed significant response rates: 9.7% overall, 18.2% in PD-L1 positive patients (PD-L1 $\geq$ 1 %) and 9% in 89 patients on maintenance treatment [32]. There were 9.9% grade 3 adverse events with 1 treatment-related death secondary to hepatic failure/autoimmune hepatitis as mentioned before [32]. Similarly, in phase 1b Keynote-012 trial, 36 metastatic gastric/gastroesophageal adenocarcinoma patients, 30 of whom had prior chemotherapy in the metastatic setting with high expression of PD-L1 (PD-L1 $\geq$ 1 %) were treated with pembrolizumab (anti PD-1 antibody) with a 22% objective response rate with 13 % grade 3 or 4 adverse events with no treatment-related death [33]. Another PD-1 antibody, nivolumab, recently showed activity in a phase III clinical trial. In this study, 493 patients with advanced gastric or gastroesophageal adenocarcinoma with progression on at least 2 prior lines of chemotherapy was randomized 2:1 to nivolumab or placebo [34]. This trial showed a significant difference in overall survival with 5.32 vs 4.14 months on nivolumab vs placebo respectively with a hazard ratio 0.63 (confidence interval: 0.50-0.78; $p < 0.0001$) [34]. However, what was more striking was with nivolumab 34.7% patients were alive at 1 year compared to 10.9% with placebo [34]. Grade 3 or more drug-related adverse events were observed in 11.5 % of patients with nivolumab compared to 5.5% on placebo [34]. These studies highlight activity of immune checkpoint blockade with the PD-1, PD-L1 axis in gastroesophageal adenocarcinomas with acceptable toxicities.

The combination of chemotherapy and immune-checkpoint blockade has not been studied in gastric and gastroesophageal adenocarcinomas, but appears to be beneficial without significantly increased toxicities. Recently, a report from a phase 2 randomized clinical trial in 123 patients with advanced non-squamous Non-Small Cell Lung Cancer (NSCLC) used a combination of carboplatin with pemetrexed and pembrolizumab compared with carboplatin with pemetrexed [35]. This trial showed an objective response rate of 55% vs 26% with combined chemotherapy and pembrolizumab verses chemotherapy arm respectively [35]. The grade 3 or worse adverse event were seen in 23 (39%) and 16 (26%) patients with combined chemotherapy and pembrolizumab verses chemotherapy arm respectively [35]. The difference in grade 3 or higher toxicities with combined chemotherapy and pembrolizumab arm was largely attributable to reduced use of steroids with pembrolizumab as there were 2 cases of grade 3 fatigue, 1 case of grade 3 nausea, 1 case of grade 3 vomiting, 2 cases of acute kidney injury and 1 case of hypokalemia [35]. However, there was also 1 case of grade 4 infusion reaction and 1 case of grade 3 pneumonitis with combined chemotherapy and pembrolizumab [35]. There was 1 treatment-related death in the combined chemotherapy and pembrolizumab arm compared to 2 deaths in the chemotherapy arm [35]. This large

phase II trial highlights benefit but more importantly safety of combined chemotherapy with immune checkpoint blockade.

Given the encouraging activity of single-agent anti-PD-1/PD-L1 antibody therapy, we are hypothesizing an additive or a synergistic effect of avelumab, an anti-PD-L1 antibody, with chemotherapy.

2.3.3 Neoadjuvant immune checkpoint blockade and surgical resectability

The addition of immune checkpoint blockade in the neoadjuvant setting does not adversely affect surgical resectability or surgical outcomes. There's currently no data available with the use of anti-PD-1 and anti-PD-L1 inhibitors in the neoadjuvant setting for gastric or gastroesophageal adenocarcinomas. However, 16 patients with Non-Small Cell Lung Cancer underwent resection following nivolumab, anti-PD-1 inhibitor, with no report of delay to surgery or surgical complications related to nivolumab [36]. Therefore, we do not anticipate that the addition of avelumab to neoadjuvant mDCF will adversely affect the surgical resection, which remains the mainstay of management of localized gastric and gastroesophageal adenocarcinomas.

3 OBJECTIVES AND PURPOSE

The primary objective is to assess the effect on the pathologic complete response (pCR), of a pre-surgery course of avelumab added to a standard chemotherapy regimen in patients with a potentially resectable, histologically-proven, adenocarcinoma or poorly differentiated carcinoma of the stomach, esophagogastric junction (EGJ), or lower third of the esophagus.

A secondary objective is to assess the effect on two-year disease-free survival (DFS), of a pre-surgery and post-surgery course of avelumab added to a standard chemotherapy regimen.

A further objective is to document the safety of adding avelumab to a standard chemotherapy regimen.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a single-center with the option to add an additional 1-2 sites, single-arm, open-label, Simon 2-stage, phase II trial in up to 55 patients with a potentially resectable, histologically-proven, adenocarcinoma or poorly differentiated carcinoma of the stomach, esophagogastric junction (EGJ), or lower third of the esophagus.

Patients will receive neoadjuvant therapy consisting of one course of 4 cycles of avelumab added to a modified chemotherapy regimen of docetaxel, cisplatin, and 5-fluorouracil (mDCF).

The disease response to neoadjuvant chemotherapy will be assessed with follow-up FDG/PET and CT scans of the chest, abdomen, and pelvis 2-4 weeks after the completion of neoadjuvant chemotherapy [37-

[45]. If there is any evidence of disease progression, patients will be reassessed by their surgeon for resectability. If they no longer have resectable disease or in the case of new metastatic cancer, patients will be offered second-line chemotherapy at the discretion of their treating oncologist. Patients with resectable disease will proceed to definitive surgery within 4-6 weeks of the completion of neoadjuvant chemotherapy.

Within 9 ± 3 weeks of surgery, another four cycles of mDCF + avelumab will be given. Patients will be followed for two years after their last dose of avelumab to assess disease-free survival rates.

The first stage of the 2-stage design will be successful if more than one of the first 16 patients shows a pCR. In that case, accrual will continue to a total of up to 55 patients. If only one patient or less has a pCR among the first 16 enrolled, the study will be closed to further accrual.

(see Schematic of Study design)

4.2 STUDY ENDPOINTS

4.2.1 Primary Endpoint

The primary endpoint is the pathologic complete response (pCR) rate after preoperative (neoadjuvant) treatment. pCR has been shown to correlate with long-term outcomes [22].

For the purpose of this study, pCR is considered to represent grade 0 and grade 1 responses, defined by the criteria of the College of American Pathologists (Table 4) [46-49].

Table 4: Tumor Regression Grade

Description	Tumor Regression Grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

Source: College of American Pathologists [48]

4.2.2 Secondary Endpoints

The secondary endpoints are the two-year disease-free survival (DFS) and the incidence of grade 3 or 4 avelumab-related adverse events.

4.2.3 Exploratory Endpoints

The correlation between circulating lymphocyte populations (B, T and NK cells) and the occurrence of immune-related adverse effects will be explored as will the correlation between tissue expression of PD-L1 and outcomes. Any finding suggestive of a correlation between biological factors and clinical outcomes will only be considered as potentially hypothesis-generating and not definitive.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Signed, informed consent;
2. Age 18 years or older;
3. Histological diagnosis of adenocarcinoma or poorly differentiated carcinoma of the stomach, esophagogastric junction (EGJ), or lower third of the esophagus;
4. The tumour must be deemed by the team to be potentially resectable. This includes imaging studies (detailed below) to clinically stage the tumor and rule out the presence of metastatic disease, and includes a preoperative laparoscopic evaluation for gastric tumors only;
5. Stage IB (T1N1 only), II, IIIA, IIIB;
6. Life expectancy greater than 3 months;
7. ECOG performance status of 0-1;
8. Neutrophils ≥ 1500/μL;
9. Platelet count ≥ 100,000/μL;
10. Hemoglobin ≥ 9 g/dL;
11. Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range unless consistent with Gilbert's syndrome (normal direct bilirubin);
12. AST and ALT ≤ 2.5 × ULN;
13. If serum creatinine above upper limit of normal (ULN), creatinine clearance ≥ 60 ml/min as determined by 24-h creatinine clearance or Cockcroft-Gault formula;
14. Negative pregnancy test for women of child-bearing potential; and
15. Highly effective contraception for both male and female subjects throughout the study and for at least 60 days after last avelumab treatment administration if the risk of conception exists

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Current or prior use of immunosuppressive medication, including corticosteroids, within 7 days prior to registration EXCEPT for the following:
    a. intranasal, intra-ocular, 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);
2. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. However, patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible;
3. Prior organ transplantation, including allogeneic stem cell transplantation;
4. Squamous-cell carcinoma diagnosis;
5. Significant acute or chronic active infections requiring systemic therapy, including, among others:
    a. Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS);
    b. Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive);
6. Vaccination with live vaccines within 4 weeks of the first dose of avelumab and while on trial;
7. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI CTCAE v 4.03) or to any component in avelumab's formulation, any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma);
8. Known severe hypersensitivity reaction to cisplatin, docetaxel, 5-FU or drugs formulated with polysorbate;
9. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication;
10. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable;

11. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study;
12. Known alcohol or drug abuse;
13. Prior systemic therapy for gastric cancer;
14. Prior exposure to antibodies directed at PD-1, PD-L1, CTLA4 antigens;
15. Pre-existing medical conditions precluding treatment, including any contraindication for major surgery;
16. Pregnancy or lactating mothers. Women of childbearing age must use contraception during and for 3 months following treatment;
17. ECOG performance status of 2 or higher;
18. Significant hearing impairment, as judged by the need for or use of a hearing aid. If there is any uncertainty regarding the degree of hearing impairment, an audiogram will be done. If the audiogram is grossly normal or shows only minor hearing impairment (i.e. not requiring hearing aid), the patient may be enrolled;
19. Unwillingness to undergo investigations and/or treatment as outlined on the study; or
20. Participation to another trial where an investigational drug is being used.
21. History of another malignancy requiring treatment within the last 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin treated curatively and in-situ cervical cancer.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The McGill University Health Centre (MUHC) is a designated provincial referral center for esophageal and gastric cancer (250-300 cases a year, of all stages, of whom 100 are operable), making advertisement for this trial relatively simple, through usual channels of communication with the medical community (Groupe d'étude en oncologie du Québec or GÉOQ, and Association des médecins hématologues et oncologues du Québec or AMHOQ.) Patients are referred by general practitioners, gastroenterologists, general surgeons and medical oncologists. For the trial, they will be approached by the medical oncologists and the surgeons listed in Section 1 *KEY ROLES.*

Taking into account strict inclusion and exclusion criteria, it is expected that about 25-30 patients a year will be enrolled, making a 2-year enrollment period plausible. Appropriate cases for the trial will be

identified through multidisciplinary tumor board discussions, held biweekly, with video links to many Quebec hospitals.

Patients will not receive any incentive for their participation to the trial. After completion of their treatment, for long-term follow-up, they will be given medical appointments, or will be contacted by phone.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from the trial at any time upon request. An investigator may terminate participation of a patient in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant; or
- The participation meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Participant Withdrawals or Termination

Patients who discontinue avelumab will be encouraged to stay on study, and will continue to be followed for safety and efficacy endpoints, unless they have withdrawn consent.

Patients who withdraw consent before surgery or who discontinue for reasons other than disease progression will be replaced, as the assessment of pathologic response is the primary objective of the trial.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause, including, but not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable; or
- Determination of futility, if, in particular, no more than one pCR is observed in the first 16 operated cases.

In any such event, the principal investigator will promptly inform the Ethics Review Board and sponsor, and will provide the reason for temporary suspension or termination. Study may resume once concerns about safety, protocol compliance, data quality, are addressed and satisfy the sponsor, the Ethics Board and the health authorities.

6 STUDY AGENT

6.1 STUDY AGENT AND CONTROL DESCRIPTION

6.1.1 Acquisition

Avelumab will be supplied free of charge by EMD Serono and shipped to the hospital pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Avelumab drug product is a clear, colorless, sterile concentrate solution for infusion.

The 20 mg/mL concentrate is provided in Ph. Eur. and 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.

6.1.3 Product 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.

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.

For infusion, the concentrate is diluted with 0.9% or 0.45% NaCl. The in-use stability for the infusion solution of avelumab has been demonstrated for 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user.

6.1.4 Preparation

For administration, avelumab drug product must be diluted with 0.9% or 0.45% NaCl.

No other drugs should be added to the solution for infusion containing avelumab.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in a manual of preparation.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequately trained personnel under a laminar flow hood using aseptic techniques:

- Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature;

- Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution;
- Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag;
- Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution;
- The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

6.1.5 Dosing and Administration

Each treatment course consists of four cycles of infusions, separated by 2 weeks. Avelumab will be administered *prior* to the chemotherapy.

In order to minize possible infusion related reactions from the administration of avelumab, patients will be premedicated prior to avelumab infusion with an antihistamine and acetaminophen.

Avelumab will be administered as an 800 mg fixed dose via 1-hour (-10/+20 minutes) IV infusion on Day 1 of each cycle (2 week cycle).

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.

Symptoms of avelumab infusion related reactions include, but are not limited to, fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria.

Patients will be instructed to report any delayed reactions to the Investigator immediately.

Following avelumab infusions on C1D4 and C2D4, patients must be observed for 30 minutes for potential infusion related reactions.

6.1.6 Route of Administration

Avelumab is only given by the intravenous route.

6.1.7 Starting Dose and Dose Escalation Schedule

No dose escalation or de-escalation schedule is planned.

6.1.8 Dose Adjustments/Modifications/Delays

See also Section 7.8 Management of Side Effects for adjustments and delays related to immune reaction adverse events.

6.1.8.1 Grade 4 ADRs

Any Grade 4 ADRs require that avelumab be discontinued except for:

- Single laboratory values out of normal range (excluding Grade 4 liver function test increase) that are unlikely related to study treatment as assessed by the investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management.

6.1.8.2 Grade 3 ADRs

Any Grade 3 ADRs require that avelumab be discontinued except for:

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

6.1.8.3 Grade 2 ADR

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

6.1.8.4 Treatment Modification for Symptoms of Infusion-Related Reactions

Grade 1 - mild

- Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- Decrease the study drug infusion rate by 50% and monitor closely for any worsening.

- The total infusion time for study drug should not exceed 120 minutes.

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.
- Stop study drug 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 the study drug infusion immediately and disconnect infusion tubing from the subject.
- Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions.

If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from study treatment.

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.

6.1.9 Duration of Therapy

All patients will receive four biweekly infusions of avelumab.

Patients undergoing surgical resection will receive a second 4-cycle course of treatment starting 9 ± 3 weeks following surgery.

6.1.10 Tracking of Dose

Dosing and adherence will be documented in both the hospital chart and the study records.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The hospital pharmacy will be responsible for receiving and dispensing all study medication.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 Study Specific Procedures

All eligible patients should be initially referred to any of the investigators, who will confirm eligibility. The necessary diagnostic workup includes:

- History & physical examination
- CT of the chest, abdomen/pelvis with intravenous iodine contrast within 4 weeks prior to enrolment
- Esophagoscopy/gastroscopy with diagnostic biopsy
- Endoscopic ultrasound within 4 weeks prior to enrolment
- Complete blood count, liver and renal profiles
- Diagnostic laparoscopy (gastric tumours only), to eliminate peritoneal disease, within 4 weeks prior to enrolment.
- PET scan within 4 weeks prior to enrolment
- Audiogram if necessary (see exclusion criteria)

The time frame to perform the above-mentioned tests can be extended by 2 weeks, at the discretion of the principal investigator

7.1.2 Standard of Care Study Procedures

All imaging studies and blood work after completion of treatment are considered standard of care.

PET will be performed before and after neoadjuvant therapy. All patients will be instructed to fast for at least 4 hours prior to the intravenous administration of ^{18}F-FDG. Imaging from the base of the skull to the upper thighs will begin approximately 60 minutes after the ^{18}F-FDG injection using a PET/CT scanner at the MUHC. After the initial imaging, the patient will be asked to drink as much water as tolerated (at least 300 mL) and regional imaging of the stomach will be acquired.

CT scan of the chest, abdomen and pelvis with iodine contrast will be performed before start of treatment, then after completion of neoadjuvant therapy for assessment of response. Radiological follow-up will continue after surgery as per protocol.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 Clinical Laboratory Evaluations

Standard of care hematology evaluations will be done. They will include a complete blood count with differential white cell count and platelet count allowing inclusion criteria 8, 9, and 10 to be assessed.

Standard of care biochemistry evaluations will be done. They will include ALT, AST, bilirubin, and creatinine allowing inclusion criteria 11, 12, and 13 to be assessed.

Pregnancy testing is also a standard of care procedure for patients receiving the mDCF regimen.

7.2.2 Other Assays or Procedures

Circulating lymphocyte populations will be assessed to allow exploratory analyses of their correlation with the occurrence of any immune-related adverse effects. Flow cytometry will be used to assess B, T and NK cells.

Tissue expression of PD-L1 will be assessed to allow exploratory analyses of its correlation with outcome.

7.3 STUDY SCHEDULE

7.3.1 Screening (Visit 1; 28 days ± 2 weeks)

- Obtain informed consent
- Demographics
- Medical history, including dysphagia score
- Physical examination
- Schedule chest/abdomen/pelvis CT with intravenous iodine contrast, FDG(^{18}F) PET, esophagoscopy/gastroscopy with diagnostic biopsy, endoscopic ultrasound, and diagnostic laparoscopy (if indicated) if not already done within 4 weeks of scheduled treatment
- EKG
- Record height, weight and vital signs
- ECOG Performance Status
- Concurrent medications
- Haematology (CBC) and Blood Chemistry (within 48 hours of C1D1)
- Free T4 and TSH (within 48 hours of C1D1)
- Hepatitis B and C testing per institutional guidelines
- Schedule audiogram if required
- Urine Pregnancy test
- AE Assessment
- Verification of inclusion/exclusion criteria (within 48 hours of C1D1)

The time frame to perform the above-mentioned tests can be extended by 2 weeks, at the discretion of the principal investigator.

-

7.3.2 Neoadjuvant Chemotherapy Phase (Visits 2 to 5;)

At each of the four visits, patients will undergo the following procedures:

- Weight and vital signs
- Physical examination
- ECOG performance status
- Concurrent medications
- Hematology and Blood biochemistry
- Urine pregnancy test
- Free T4 and TSH on the first and last cycle only
- Avelumab 800 mg fixed dose prior to the infusion of the ~~following completion of the~~ mDCF regimen
- Docetaxel as a one-hour 40 mg/m^2 IV infusion on day 1
- Cisplatin 40 mg/m^2 IV infusion on day 1
- 5-FU 1000 mg/m^2/day over 2 days
- Patients will see their treating physician within 48 hours of each treatment administration.

7.3.3 Imaging Assessment of Response (Visit 6;)

The disease response to neoadjuvant chemotherapy will be assessed with follow-up FDG/PET and CT scans of the chest, abdomen, and pelvis with intravenous iodine contrast 2 to 4 weeks after the completion of neoadjuvant chemotherapy. If there is any evidence of disease progression, patients will be reassessed by their surgeon for resectability. If they no longer have resectable disease or in the case of new metastatic cancer, patients will be offered second-line chemotherapy at the discretion of their treating oncologist.

7.3.4 Surgery (Visit 7;)

Patients with resectable disease will proceed to definitive surgery within 4 to 6 weeks of the completion of chemotherapy. The treating surgeon will decide the type of surgical resection. A D2 celiac lymph node dissection will be recommended, however the actual procedure performed will be at the discretion of the treating surgeon.

The resected tumor and lymph nodes will be assessed for the presence of cancer cells.

Prior to surgery, the following procedures will be done:

- Weight and vital signs
- ECOG performance status
- Concurrent medications
- Hematology and Blood biochemistry

- AE assessment

7.3.5 Adjuvant Chemotherapy Phase (Visits 8 to 11)

Within 6 to 12 weeks following surgery, another four cycles of mDCF + avelumab will be restarted according to the same schedule as above. Chemotherapy treatment must be given even if the treating investigator elects to remove Avelumab from the regimen. This should be discussed with the sponsor, Dr Thierry Alcindor.

At each of the four visits, patients will undergo the following procedures:

- Weight and vital signs
- ECOG performance status
- Concurrent medications
- Hematology and Blood biochemistry
- Urine pregnancy test
- Free T4 and TSH (prior to the first cycle only)
- ECG (prior to the first cycle only)
- Avelumab 800 mg fixed dose prior to the infusion of the mDCF regimen
- Docetaxel as a one-hour 40 mg/m^2 IV infusion on day 1
- Cisplatin 40 mg/m^2 IV infusion on day 1
- 5-FU 1000 mg/m^2/day over 2 days
- Patients will see their treating physician within 48 hours of each treatment administration.

7.3.6 Final Study Visit (Visit 12)

The final study visit will be approximately 30 days (± 7 days) after the last treatment administration and/or surgery. The following procedures will be done at this visit:

- Physical exam
- Weight and vital signs
- ECOG performance status
- Concurrent medications
- Hematology and Blood biochemistry
- Free T4 and TSH.
- AE assessment

7.3.7 Follow-up

Patients will be assessed in person or via a telephone call approximately 90 days (± 7 days) after the last administration of avelumab. In case of concerns about delayed immune reactions, the patient will be given a medical appointment for full assessment.

Patients will continue to be regularly monitored by visits and radiological assessments, which can be done at the MUHC or at any medical facility for the patient's convenience.

Standard-of-care follow up consists of:

- a CT of the chest, abdomen, and pelvis with intravenous iodine contrast every 3 months for 2 years
- endoscopy at 6, 12, and 24 months

7.3.8 Early Termination Visit

When a participant has discontinued the investigation product and/or participation in the study, the following procedures should be undertaken:

- Physical exam
- Weight and vital signs
- ECOG performance stat
- Haematology and blood biochemistry
- Free T4 and TSH
- AE Assessment

In the case of discontinuation of treatment, safety follow-up shall continue at 30 days and 3 months as per table 7.3.11 assuming the patient is agreeable to continue follow-up.

7.3.9 Unscheduled Visit

The purpose and findings of any unscheduled visit will be recorded in the case report form.

7.3.10 Schedule of Events Table

			mDCF + avelumab						mDCF + avelumab				Post-treatment f/u		
Weeks	0 to 28														
Procedure	Visit 1 Screen		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 Surgery	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 30-day f/u	Visit or Telephone	2-year Follow-up
Consent	x														
Demographics	x														
Medical history	x														
Physical exam	x												x		
Diagnostic procedures[1]	x														
CT chest/abdomen/pelvis	x						x							x[5]	x
FDG(^{18}F) PET	x						x								
Audiogram [2]	x														
ECG	x								x						
Height	x														
Weight/Vital signs	x		x	x	x	x	x	x	x	x	x	x	x		
Performance status	x		x	x	x	x	x	x	x	x	x	x	x		
Concurrent medications	x		x	x	x	x	x	x	x	x	x	x	x		
Hematology/Biochemistry[7]	x		x	x	x	x	x	x	x	x	x	x	x		
Pregnancy test [3]	x		x	x	x	x			x	x	x	x	x		
Review inc/exc criteria[7]															
Free T4, TSH [4]						x			x				x		
mDCF + avelumab			x	x	x	x			x	x	x	x			
Surgery & histology								x							
Adverse event evaluation			←												→
Endoscopy[6]															x

* Post-treatment follow-up visits at 30 and 90 days (only 90-day visit includes CT scan)

1: Diagnostic biopsy, endoscopic ultrasound, and diagnostic laparoscopy (for gastric tumours only)

2: As clinically indicated throughout;

3: Urine pregnancy test for women of childbearing potential must be performed at baseline and least every month during treatment;

4: Free T4 and TSH must be measured at screening, at least every 48 weeks during treatment, and at end of treatment or at the 30-day post-treatment follow-up (if not performed in the previous 8 weeks).

5. Every three months

6. 6, 12, 24 months

7. Within 48 hours of C1D1

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Patients will be queried at each visit regarding concomitant medications. All concomitant medications, prescription and non-prescription, taken during the study will be recorded on the case report forms (CRFs).

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

None.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Prior to the infusions of avelumab, subjects will be pre-treated with an H_1-antihistamine (e.g., diphenhydramine 50 mg) and acetaminophen (650 mg) approximately 30 to 60 minutes prior to avelumab..

Prophylactic dexamethasone 10-12 mg will be taken prior to docetaxel infusion to prevent fluid retention and reduce the likelihood of allergic response.

Standard anti-emetic prophylaxis and continuing treatment will be provided prior to cisplatin.

Prophylactic filgastrim (5 mcg/kg/day SC x 5-10 days) or pegfilgastrim (6 mg sc x 1 day, if available) will be given at the discretion of the investigators, 24 hours after the completion of the 5-FU infusion.

7.8 MANAGEMENT OF SIDE EFFECTS

7.8.1 Management and Dose Modifications for mDCF

Doxetaxel, cisplatin, and 5-FU will be given as described in 7.3.3 Neoadjuvant Chemotherapy.

Toxicity will be graded according to National Cancer Institute Common Toxicity Criteria (CTC) Version 4.0.3.

Imodium will be prescribed to treat 5-FU-induced diarrhea with addition of octreotide in severe (> grade 2) cases. Steroids will be given if there is no rapid resolution of the diarrhea. The dose of 5-FU will reduced by 25% at any time for CTC grade 3 or greater diarrhea or mucositis, and CTC grade 2 or greater hand and foot syndrome. Administration of cisplatin, docetaxel, and 5-FU will be delayed as long as there is diarrhea or mucositis of CTC grade 2 or greater, or thrombocytopenia less than 75,000/μL (grade 2).

The dose of cisplatin will be reduced by 50% if the creatinine clearance (Gault-Cockroft) decreases to between 50 and 60 mL/min. Cisplatin will be discontinued if the creatinine clearance falls to less than 50 mL/min, or if there is peripheral neuropathy of CTC grade 3 or greater.

The dose of docetaxel will be reduced by 25% in case of CTC grade 4 neutropenia persisting longer than 7 days or accompanied by fever and thrombocytopenia of CTC grade 3 or greater. Docetaxel will be discontinued in the case of a severe hypersensitivity reaction or bilirubin level more than 2 ULN, or of peripheral neuropathy of CTC grade 3 or greater.

Any of drugs will be discontinued in the event of a delay by more than two weeks due to drug-specific toxicity.

7.8.2 Management and Dose Modifications for Avelumab

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similarly to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

Treatment of gastrointestinal, dermatological, pulmonary, hepatic and endocrine irAEs should follow guidelines set forth below.

7.8.2.1 Gastrointestinal irAEs

Grade 1

Description:	• Diarrhea: < 4 stools/day over baseline • Colitis: Asymptomatic
Management	• Continue avelumab therapy • Symptomatic treatment (for example, loperamide)
Follow-up	• Close monitoring for worsening symptoms • Educate subject to report worsening immediately • If worsens, treat as Grade 2 or 3/4

Grade 2

Description:	• Diarrhea: 4 to 6 stools per day over baseline • IV fluids indicated < 24 hours • Not interfering with ADL • Colitis: abdominal pain, blood in stool
Management	• Delay avelumab therapy • Symptomatic treatment
Follow-up	• If improves to Grade 1: resume avelumab therapy

- If persists > 5 to 7 days or recurs, give 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent
- When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol.
- If worsens or persists > 3 to 5 days with oral steroids, treat as Grade 3 to 4

Grade 3 to 4

Description:
- Diarrhea (Grade 3): ≥ 7 stools per day over baseline
- Incontinence
- IV fluids ≥ 24 hours
- Interfering with ADL
- Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs
- Grade 4: life-threatening, perforation

Management
- Discontinue avelumab therapy
- 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider lower endoscopy

Follow-up
- If improves, continue steroids until Grade 1, then taper over at least 1 month
- If persists > 3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

7.8.2.2 Dermatological irAEs

Grade 1 to 2

Description:
- Covering ≤ 30% body surface area

Management
- Symptomatic therapy (for example, antihistamines, topical steroids)
- Continue avelumab therapy

Follow-up
- If persists > 1 to 2 weeks or recurs: consider skin biopsy
- Delay avelumab therapy
- Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent
- Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
- If worsens, treat as Grade 3 to 4

Grade 3 to 4

Description:	• Covering > 30% body surface area; life threatening consequences
Management	• Delay or discontinue avelumab therapy • Consider skin biopsy • Dermatology consult • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent
Follow-up	• If improves to Grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume avelumab therapy

7.8.2.3 Pulmonary irAEs

Grade 1

Description:	• Radiographic changes only
Management	• Consider delay of avelumab therapy • Monitor for symptoms every 2 to 3 days • Consider pulmonary and infectious disease consults
Follow-up	• Re-image at least every 3 weeks • If worsens, treat as Grade 2 or Grade 3 to 4

Grade 2

Description:	• Mild to moderate new symptoms
Management	• Delay avelumab therapy • Pulmonary and infectious disease consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy
Follow-up	• Re-image every 1 to 3 days • If improves, when symptoms return to near baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics • If not improving after 2 weeks or worsening, treat as Grade 3 to 4

Grade 3 to 4

Description:	• Severe new symptoms; new/worsening hypoxia; life-threatening
Management	• Discontinue avelumab therapy • Hospitalize • Pulmonary and infectious disease consults

- 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider bronchoscopy, lung biopsy

Follow-up
- If improves to baseline, taper steroids over at least 6 weeks
- If not improving after 48 hours or worsening: add immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

7.8.2.4 Hepatic irAEs

Grade 1

Description:
- Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN

Management
- Continue avelumab therapy

Follow-up
- Continue liver function monitoring
- If worsens, treat as Grade 2 or 3 to 4

Grade 2

Description:
- AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN

Management
- Delay avelumab therapy
- Increase frequency of monitoring to every 3 days

Follow-up
- If returns to baseline, resume routine monitoring, resume avelumab therapy
- If elevations persist > 5 to 7 days or worsen, 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy

Grade 3 to 4

Description:
- AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN

Management
- Discontinue avelumab therapy
- Increase frequency of monitoring to every 1 to 2 days
- 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consult gastroenterologist
- Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted

Follow-up
- If returns to Grade 2, taper steroids over at least 1 month

- If does not improve in > 3 to 5 days, worsens or rebounds, add mycophenolate mofetil 1 gram (g) twice daily
- If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

7.8.2.5 Cardiac irAEs

Description:
- 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

Management
- Withhold avelumab therapy
- 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

Follow-up
- If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy
- 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

Description:
- Immune-mediated myocarditis

Management
- Permanently discontinue avelumab
- Guideline based supportive treatment as appropriate as per cardiology consult**Error! ookmark not defined.**
- Methylprednisolone 1 to 2 mg/kg/day

Follow-up
- Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
- If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)

7.8.2.6 Endocrine irAEs

Description:
- Asymptomatic TSH abnormality

Management
- Continue avelumab therapy

Follow-up
- If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements, include T4 at subsequent cycles as clinically indicated
- Consider endocrinology consult

Description:
- Symptomatic endocrinopathy

Management
- Evaluate endocrine function
- Consider pituitary scan
- Symptomatic with abnormal lab/pituitary scan:
  - Delay avelumab therapy
  - 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent
  - Initiate appropriate hormone therapy
  - Endocrinology consult to distinguish (differentiate) between primary from secondary dysfunction
- No abnormal lab/pituitary MRI scan but symptoms persist:
  - Repeat labs in 1 to 3 weeks/MRI in 1 month

Follow-up
- If improves (with or without hormone replacement):
  - Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
  - Resume avelumab therapy
- Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Description:
- Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)

Management
- Delay or discontinue avelumab therapy
- Rule out sepsis
- Stress dose of iv steroids with mineralocorticoid activity
- iv fluids
- Consult endocrinologist
- If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.1.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 Severity of Event

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.

- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

The investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Patients will be assessed in person or by telephone approximately 90 days (± 7 days) after the last administration of avelumab.

8.4 REPORTING PROCEDURES

8.4.1 Adverse Event Reporting

Adverse events will be recorded in the CRF by the clinical research associate or the research nurse and signed off by the investigator within 10 days.

8.4.2 Serious Adverse Event Reporting

The Sponsor-Investigator primary responsibilities for safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and EMD Serono, as required by local regulations (for regulatory reporting) and as required by the ISS agreement (for reporting to EMD Serono).

The following reportable events must be submitted to EMD Serono within 24 hours (or immediately for death or life-threatening events) using the applicable safety report form provided:

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

Reports may be sent by fax +49 6151 72 6914 or e-mailed to GlobalDrugSafety@merckgroup.com

In addition to the SAE description, reports should include the protocol number, the subject number, the study site, the principal investigator's name, and clearly specify the date of onset.

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor and Research Ethics Board within 24 hours of site awareness. See Section 1, Key Roles for contact information.

Other SAEs, regardless of relationship, will be submitted to the Research Ethics Board and study sponsor within 72 hours of site awareness.

The principal investigator will supply the sponsor, McGill Institutional University Health Centre's Ethics Review Board and Health Canada with as much of the following information that is available at the time of the initial phone call:

- Patient Demographics: patient identification (number), sex, date of birth, race
- Study Identification: protocol number, investigator name, study diagnosis
- Study Drugs: drug code or drug name, unit dose (if known), total daily dose (if known), frequency, route, start date, date of injection
- Adverse Event: description, date of onset, severity, chronicity, treatment, (including hospitalization), action taken with respect to test drug, clinical significance, test results (if applicable)
- Relation to test drug: concomitant drug therapy at time of adverse event, indication, total daily dose, duration of treatment
- In case of death: cause, autopsy findings (if available)

The study sponsor will be responsible for notifying regulatory bodies of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their Research Ethics Board and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the Research Ethics Board project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the Research Ethics Board and to the study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the Research Ethics Board and to the study sponsor within 7 days of the investigator becoming aware of the problem.

8.4.4 Events of Special Interest

Not applicable

8.4.5 Reporting of Pregnancy

In order to participate to the trial, patients must use a highly effective contraceptive method, or be unable to procreate. In the case of a pregnancy, study treatment will be stopped immediately, and permission will be requested from the pregnant patient to let the investigator continue follow-up for assessment of safety and pregnancy outcomes. If pregnancy is confirmed in a study subject during the course of a clinical trial, the continued administration of study drug must be evaluated immediately. Study drugs should be discontinued. The investigator must immediately notify the Health Canada and record the pregnancy on the pregnancy surveillance form(s). In addition, the investigator must report to Health Canada follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks.

8.5 STUDY HALTING RULES

The study will be halted if among the first 16 patients, six nonhematological Grade 4 AEs determined to be probably related are reported. The Research Ethics Board will be notified within 24 hours of this occurrence and will decide, after review, to allow, or not, resumption of the trial.

As described in section 10 *STATISTICAL CONSIDERATIONS*, the study will be terminated if there is no more than one pathological complete responses among the first 16 patients.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the Research Ethics Board to which safety reports will be sent twice a year.

9 CLINICAL MONITORING

Throughout the conduct of the trial, on-site monitoring for this study will be performed by personnel from The Research Institute of the McGill University Health Centre (RI-MUHC). It will consist in targeted data verification of efficacy and safety endpoints, and the distribution of monitoring reports to the principal investigator. There will be no planned external audit. The standard operative procedures (SOP) of the Centre for Innovative Medicine (RI-MUHC) will be followed to ensure quality management of study conduct, data collection, documentation and completion.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

There will be no formal statistical and analytical plan (SAP), as the statistical considerations pertaining to this trial are laid out in this protocol.

10.2 STATISTICAL HYPOTHESES

H_0: The addition of avelumab to chemotherapy will result in a 7% pCR rate.

H_1: The addition of avelumab to chemotherapy will result in a 20% or greater pCR rate

10.3 ANALYSIS DATASETS

The following datasets will be analyzed to report the various outcomes of the present study:

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all registered participants)
- Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one dose of investigational product and underwent surgery)
- Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of investigational product)
- Evaluable or Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of treatment according to the underlying scientific model

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 General Approach

This is a single-arm phase II study testing the incorporation of avelumab to standard chemotherapy, with plans to compare the obtained complete pathologic response rate with historical data (patients treated with chemotherapy only).

10.4.2 Analysis of the Primary Efficacy Endpoint

The pathologic complete response rate (pCR rate) is the primary efficacy endpoint in this trial. For the purpose of the study, pCR is defined as complete absence or near-complete absence of cancer cells (less than 10% viable cells) in the resected tumor and lymph nodes. It is a single endpoint.

The Modified Intention-to-Treat Analysis Dataset will be used for analysis of the primary efficacy endpoint (e.g., participants who took at least one dose of investigational product and underwent surgery). Any patient who experiences early disease progression or dies of progressive disease prior to surgery will be considered as having an incomplete surgical resection and will be excluded from the primary endpoint analysis but will be included for secondary endpoint analyses

10.4.3 Analysis of the Secondary Endpoint

The Kaplan-Meier method will be used to estimate the distribution of time to events including DFS.

10.4.4 Safety Analyses

All patients who receive at least one cycle of therapy must be considered assessable for toxicity. Therefore, the Safety Analysis Dataset defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of investigational product). Adverse events will be counted once only for a given participant and will be described according to the NCI Common Toxicity Criteria version 4.0. They will be assessed by the investigator as related or not related. Summary statistics during treatment will be collected in CRFs and periodically analyzed.

Adverse events will be reported by the investigator, as described above. Adverse events leading to premature discontinuation from the study drug and serious treatment-emergent AEs will be presented either in a table or a listing. The perioperative complication rate will be analyzed as well.

10.4.5 Adherence and Retention Analyses

Not applicable

10.4.6 Baseline Descriptive Statistics

As this is a single-arm study, demographic and laboratory characteristics of study patients will be recorded and described, with no plans for comparison.

10.4.7 Planned Interim Analyses

10.4.7.1 Safety Review

If six or more Grade 4 adverse events (other than hematological) are noted among the first 16 patients, the study will be temporarily halted and the safety data submitted to the Research Ethics Board, until a further decision is made.

10.4.7.2 Efficacy Review

After the first 16 patients have undergone surgery, an interim analysis for efficacy will be performed. The study will be stopped if there is not more than one case of pCR.

10.4.8 Additional Sub-Group Analyses

Not applicable

10.4.9 Multiple Comparison/Multiplicity

Not applicable

10.4.10 Tabulation of Individual Response Data

Individual patient data will be stored in the study database, but will not be listed by measure and time point.

10.4.11 Exploratory Analyses

The correlation between circulating lymphocyte populations and the occurrence of immune-related adverse effects will be analyzed.

The correlation between PD-L1 and outcomes will also be analyzed.

10.5 SAMPLE SIZE

The DCF chemotherapy combination, when given perioperatively to patients with resectable gastric/EGJ adenocarcinoma, results in a pCR rate inferior to 10% and a 5-year survival of approximately 50%. Given the postulated synergy between chemotherapy and anti-PD-L1 antibody immunotherapy, it is

hypothesized that, in comparison to a 7% pCR rate with mDCF/DCF (null hypothesis), a 20% pCR rate will be observed in patients receiving the experimental combination, mDCF/avelumab (alternate hypothesis). Fifty patients will be enrolled in a Simon 2-stage scheme to achieve a statistical power of 80%, with α error of 5%: the first stage will be successful if at least one in 16 treated patient shows pCR; in that case, accrual will continue to a total of 50 patients, and the study will be considered positive if at least 6 patients achieve pCR [50]. If no more than one patient has pCR among the first 16 enrolled, the study will be closed to further accrual. The data of all patients who have received at least one cycle of treatment before surgery will be analyzed for safety and efficacy.

10.6 MEASURES TO MINIMIZE BIAS

Not applicable.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Appropriate medical and research records for this trial will be maintained, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Authorized representatives of regulatory agencies will be allowed to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki and applicable Canadian law.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Research Ethics Board (REB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 Consent Procedures and Documentation

Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be approved by the Research Ethics Board and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Patients will be offered the alternative option of being treated off protocol with standard neoadjuvant chemotherapy prior to surgery or immediate surgery followed by combined chemotherapy and radiation at the discretion of the treating physician

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the Research Ethics Board and the institutional regulations of the McGill University Health Centre (MUHC.) Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Research Institute of the MUHC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the MUHC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Research Institute of the MUHC

13.4.1 Research Use of Stored Human Samples, Specimens or Data

Samples and data collected under this protocol may be used for experiments mentioned in section. No germline genetic testing will be performed.

Access to stored samples will be limited to the staff of research laboratories under the direction of investigators and named collaborators of the trial. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

Data will be tracked using standard software to that effect.

All stored samples will be kept in research laboratories of the MUHC. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5 FUTURE USE OF STORED SPECIMENS

After completion of the study, stored specimens will be discarded.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator (PI). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Erasing, overwriting, and the use of correction fluid or tape on the original are not allowed.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record. Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap a 21 CFR Part 11-compliant data capture system provided by Harvard Catalyst. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

The retention of study records will be done according to Health Canada regulations, that is for 25 years.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff.

As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 15 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and sent to the local Research Ethics Board (REB) per their guidelines. The site PI/study staff is responsible for knowing and adhering to their REB requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

This trial will be registered in an internationally recognized repository, such as clinicaltrials.gov, and its results published in a peer-reviewed journal. Authors will include investigators and collaborators who have made a significant contribution to the design or execution of the trial or analysis of the trial results.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Principal Investigator and at least another investigator whom he shall name will constitute a steering committee for the conduct of the study. They will meet in person at least twice a year.

16 CONFLICT OF INTEREST POLICY

All study investigators will disclose any real or potential conflict of interest.

17 LITERATURE REFERENCES

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