VANDERBILT UNIVERSITY
MEDICAL CENTER

A Pilot Study to Investigate the Safety and Efficacy of Avelumab Monotherapy in Patients with Advanced or Metastatic Adenocarcinoma of the Small Intestine VICC GI 1679

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1. SYNOPSIS

Sponsor	Vanderbilt University Medical Center
Protocol Title	*A Pilot Study Investigating the Safety and Efficacy of Avelumab Monotherapy in Patients with Advanced or Metastatic Adenocarcinoma of the Small Intestine.*
Protocol Number	VICC LOI 16001
Phase of Development	Phase 2 pilot study
Investigational Product and Mechanism	Avelumab (MSB0010718C), a fully human IgG1 antibody directed against the programmed death ligand 1 (PD-L1).
Treatment Schedule	10 mg/kg avelumab, as 1-hour intravenous (IV) infusion every 2 weeks (Q2W).
Objectives	Primary Objective • To describe any antitumor activity of avelumab monotherapy, as measured by the response rate in patients with advanced or metastatic small intestinal adenocarcinoma. • To describe the safety profile of avelumab monotherapy in patients with advanced or metastatic small intestinal adenocarcinoma. Secondary Objectives • To determine overall survival, progression-free survival, and duration of response of avelumab monotherapy in patients with advanced small intestinal adenocarcinoma. • To evaluate the association of tumor PD-L1 and PD-1 expression, MSI status, lymphocytic infiltration, and somatic mutation burden with response.
Trial Design	This is a single-agent, open label, one-arm phase 2 pilot study of avelumab in patients with advanced or metastatic adenocarcinoma of the small intestine.
Estimated Number of Patients	This investigator-initiated study intends single-site enrollment limited to patients at Vanderbilt University Medical Center. About 25 patients evaluable for disease response are anticipated to enroll in about 30 months.
Length of Study	It is intended that patients will be treated until disease progression or intolerable toxicity.
Investigational Product Dose/Route/Regimen	Treatment will consist of Cycles lasting 2 weeks (14 days) each. Investigational avelumab will be provided by EMD Serono Research & Development Institute, Inc. Patients will be treated with 10 mg/kg avelumab once every 2 weeks (Q2W), which is identical to the dose regimen presented in the 2015 American Society of Clinical Oncology (ASCO) abstract[1] of the avelumab phase I study in advanced solid tumors (NCT01772004).
Study Assessments	See the Schedule of Assessments in Section 7.

2. STUDY DESIGN

2.1. Summary

This is a single-agent, open label, one-arm, single-institution phase 2 pilot study of avelumab in patients with advanced or metastatic adenocarcinoma of the small intestine.

Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against the programmed death ligand 1 (PD-L1). Avelumab binds to PD-L1 and blocks the interaction between PD-L1 and its receptor PD-1. Antibody-mediated binding of PD-L1 by avelumab removes the suppressive association of the PD-L1 ligand with the PD-1 receptor expressed by anti-tumor CD8+ T cells, thus restoring a cytotoxic T cell response.

Our laboratories demonstrated PD-1 and PD-L1 expression in a significant percentage of small bowel adenocarcinomas (85% and 45%, respectively). Additionally, there are a significant number of patients with MSI-high phenotype as well as high levels of CD3+, CD4+ and CD8+ T cells. Therefore, we propose a pilot study to evaluate the efficacy of the anti-PD-L1 antibody avelumab, in patients with advanced small intestinal adenocarcinoma who have received any number of prior chemotherapeutic regimens or who have recurrent disease.

Because of the known role of PD-L1 in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, antibody-mediated therapeutic blockade of the PD-L1/PD-1 interaction presents a promising strategy for oncologic immunotherapy.

2.2. Scientific Rationale and Hypothesis

We recently presented preliminary data (see Section 4.3 for additional detail) at the 2016 Gastrointestinal Cancers Symposium suggesting that small intestinal adenocarcinomas might benefit from a programmed death 1 (PD-1) pathway inhibitor.[2] Immunohistochemistry (IHC) for the expression of PD-L1 and PD-1 was performed on archived tissue samples of small intestinal adenocarcinomas. We observed strong PD-L1 expression in 12 of the 26 cases (46%), which is similar to a previous study reporting strong PD-L1 staining in 50% of their small intestinal adenocarcinoma cohort.[3]

All tumor samples with strong PD-L1 expression also had tumor surrounding lymphocytes, lymphoid aggregates, and tumor infiltrating lymphocytes (TILs) that expressed PD-1. These results suggest that PD-L1 and PD-1 are expressed in a majority of small intestinal adenocarcinomas, and that inhibition of PD-L1 might be an attractive treatment option for this patient population where effective therapeutic options for advanced disease are limited.

Based on the data suggesting approximately 50% of small intestinal adenocarcinomas exhibit strong expression of PD-L1, we propose a pilot study to evaluate efficacy of the PD-L1 antibody avelumab in patients with advanced or metastatic small intestinal adenocarcinoma who have received any number of prior chemotherapeutic regimens or who have recurrent disease.

This study will focus on the antitumor activity as measured by response rate, as well as describe the safety profile of avelumab monotherapy in this patient population. Secondary objectives include the determination of overall survival and progression-free survival in this population. Available tumor tissue from an archival block or from a medically safe fresh biopsy will be required for study entry. PD-L1 expression levels using immunohistochemistry will be prospectively correlated with clinical benefit from avelumab. Microsatellite instability (MSI) status and lymphocyte infiltration analysis will also be prospectively correlated with clinical benefit.

It is hypothesized that avelumab monotherapy in patients with advanced or metastatic small intestinal adenocarcinoma will be safe and that observed clinical response to avelumab in patients with advanced small intestinal adenocarcinoma will not be inferior to standard-of-care chemotherapy regimens.

2.3. Treatment and Dose Rationale

Investigational avelumab will be provided by EMD Serono Research & Development Institute, Inc.

Treatment will consist of cycles lasting 14 days (2 weeks). Each patient will be treated with 10 mg/kg avelumab, administered as 1-hour intravenous (IV) infusion once every two weeks (Q2W).

As additionally addressed below in Section 4.5, based on pharmacokinetic, pharmacodynamic, receptor occupancy, and preliminary clinical safety and efficacy data, biweekly 10 mg/kg is the recommended dose administered to more than 480 patients in the ongoing dose-expansion phase of study EMR 100070-001 (NCT01772004): *A Phase I, Open-label, Multiple-ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of Avelumab (MSB0010718C) in Subjects With Metastatic or Locally Advanced Solid Tumors and Expansion to Selected Indications*.

Avelumab will be administered on Day 1 of each cycle after all assessments and procedures have been completed as described in the Schedule of Assessments table (Section 7). In general, it intended that patients will be treated until disease progression or intolerable toxicity.

3. OBJECTIVES

3.1. Primary Objectives

- To describe any antitumor activity of avelumab monotherapy, as measured by the response rate in patients with advanced or metastatic small intestinal adenocarcinoma.
- To describe the safety profile of avelumab monotherapy in patients with advanced or metastatic small intestinal adenocarcinoma.

3.2. Secondary Objectives

- To determine overall survival, progression-free survival, and duration of response of avelumab monotherapy in patients with advanced small intestinal adenocarcinoma.
- To evaluate the association of tumor PD-L1 and PD-1 expression, MSI status, lymphocytic infiltration, and somatic mutation burden with response.

4. BACKGROUND

4.1. Small Intestinal Adenocarcinoma

Although the small intestine makes up about 75% of the length of the digestive tract and 90% of its mucosal surface area, cancer of the small intestine is rare, representing only 5% of all gastrointestinal cancers.[4] However, according to the United States National Cancer Database, the incidence of small intestinal cancers has approximately doubled since the 1970s.[5] In the small intestine, four histological types of cancers predominate: adenocarcinomas, neuroendocrine tumors, gastrointestinal stromal tumors, and lymphomas. This clinical trial will focus on adenocarcinoma of the small intestine.

Small intestinal adenocarcinoma represents approximately one-third of all small intestinal cancers, and it was estimated that approximately 3,200 new cases would be diagnosed in the United States in 2015.[6] Adenocarcinomas are found throughout the entire small intestine, however more than half are located in the duodenum.[5,7] Due to the rarity of the disease and anatomical proximity to the large bowel, small intestinal adenocarcinomas are frequently grouped with, and thus often treated like, large intestinal adenocarcinomas. However, small intestinal cancers have a very different microenvironment compared to large intestinal cancers and will thus most likely respond differently to the same therapies thus potentially lowering the efficacy of these treatments.

Patients presenting with localized disease are treated with complete resection of the primary tumor with locoregional lymph node resection. However, due to nonspecificity of symptoms at presentation, a majority of the patients are diagnosed with advanced disease, where 5-year survival drops from 65% at stage I to 4% for stage IV.[8] Furthermore, a study observed that 37% of patients with primary tumor resection experienced recurrent disease with a median time to recurrence of 1.3 years, and a majority of patients with recurrent disease had distant metastasis.[9]

Systemic chemotherapy is regarded as the standard treatment option for patients with metastatic or recurrent disease despite the lack of prospective, randomized trials evaluating the role of palliative chemotherapy for the treatment of this patient population. A combined analysis of several retrospective studies observed a median overall survival of 13 months for patients receiving systemic chemotherapy, versus 4 months in those patients treated with best-supportive care alone.[10] Three prospective studies using three different regimens, all with oxaliplatin as the backbone chemotherapy, observed response rates of 39%-50% and median overall survival of 12.7-20.4 months.[11-13] As a second line therapy, FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) was shown to have a disease control rate of 52% though response rate was only 20% and median progression-free survival was 3.2 months.[14]

Despite the observed survival advantage, the published studies are not randomized prospective trials and suffer from small, heterogeneous patient populations and selection bias. Additionally, the role of targeted agents, such as the anti-EGFR therapies commonly used in colorectal cancer, has not been established for the treatment of small intestinal adenocarcinomas. Furthermore, no approved therapies exist, as large-scale phase III studies are problematic due to the rarity of the disease. Exploring innovative clinical trial designs with novel treatment strategies is therefore vital to improve clinical outcomes for patients with adenocarcinomas of the small intestine.

4.2. PD-L1

The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions.[15-17] PD-L1 (also called B7-H1 and CD274) can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells; and PD-L1 expression is greatly up-regulated after activation or interferon treatment.[16] Numerous results from in vitro cellular assays have demonstrated that blockade of the PD-1/PD-L1 interaction enhances T cell responses, such as increases in proliferation and cytokine production.[18-24] In PD-$1^{-/-}$ mice both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies.[25,26] Breaking tolerance via blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance T cell activity towards chronic pathologies such as cancer.[27]

Immunohistochemistry studies[26] have demonstrated that PD-L1 is also expressed by a variety of human tumors, both by the tumor cells, as well as by the immune cells that are present in the tumor microenvironment. In contrast to very strong expression on syncytiotrophoblasts in the placenta and in cancer cells, low levels of PD-L1 expression were detected in some normal tissues including fetal cardiac tissue.[20] High levels of PD-L1 expression have been found to be associated with disease progression, increased metastasis, poor response to treatment, and decreased survival in a number of human cancers.[26] Importantly anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effects in combinatorial therapy.[19,28-33]

4.3. Correlative Science

Our preliminary data suggest that inhibition of PD-L1 might be an attractive treatment option in small bowel adenocarcinoma (SBA) because PD-L1 and PD-1 are expressed in a majority of small intestinal adenocarcinomas.[2] We performed immunohistochemistry (IHC) analysis of PD-L1 and PD-1 expression on archived tissue samples of small intestinal adenocarcinomas and observed strong PD-L1 expression in 12 of the 26 cases (46%) that was localized to the macrophages around the tumor invasive front and in some of the tumor cells adjacent to the macrophages (**Figure 1**). All tumor samples in our cohort with strong PD-L1 expression also had PD-1 expressing tumor infiltrating lymphocytes (TILs) and PD-1 positive lymphocytes and lymphoid aggregates surrounding the tumor. These data are consistent with a previous study that reported robust PD-L1 staining in 50% of small intestinal adenocarcinomas.[3] Interestingly, results of a Phase I study of MPDL3280A (anti-PD-L1) in patients harboring a wide range of tumors indicated that responses were observed in pre-treatment tumors expressing high levels of PD-L1, especially when PD-L1 was expressed by TILs.[34,35] In that study PD-L1 positive tumor-infiltrating immune cells were more common than PD-L1 positive tumor cells at baseline. Based on these data we propose to perform PD-L1 and PD-1 IHC in SBA (n=25), prior to treatment with avelumab, to test the hypothesis that PD-L1 and PD-1 positive staining in the tumor and TILs correlates with disease response to PD-L1 inhibition.

In addition to PD-L1 staining, we propose to evaluate the presence of immune cells (e.g. CD3+, CD4+, and CD8+) in and surrounding pre-treatment tumors by IHC. We hypothesize that increased TILs at baseline will correlate with response to PD-L1 inhibition. Results from the MDPL3280A phase I study suggests that PD-L1 inhibition is most effective when pre-existing immunity is suppressed by PD-L1, and is re-invigorated on antibody treatment.[35] Our preliminary data indicate that small intestinal adenocarcinomas expressing PD-L1 contained more CD3+, CD4+, and CD8+ tumor infiltrating T cells than those without expression of PD-L1 (**Figure 1** and **Table 1**). In our

tumors, there were approximately 3 times more CD4 cells than CD8 cells. These data are consistent with a previous report in melanoma that showed PD-L1 expression associated with a higher density of CD3+ TILs.[36] In addition to or alternative to immune cell staining, IHC for other cell types may also be performed on the tumor specimens if new clinical or pre-clinical data emerge that unveil novel biomarkers of response.

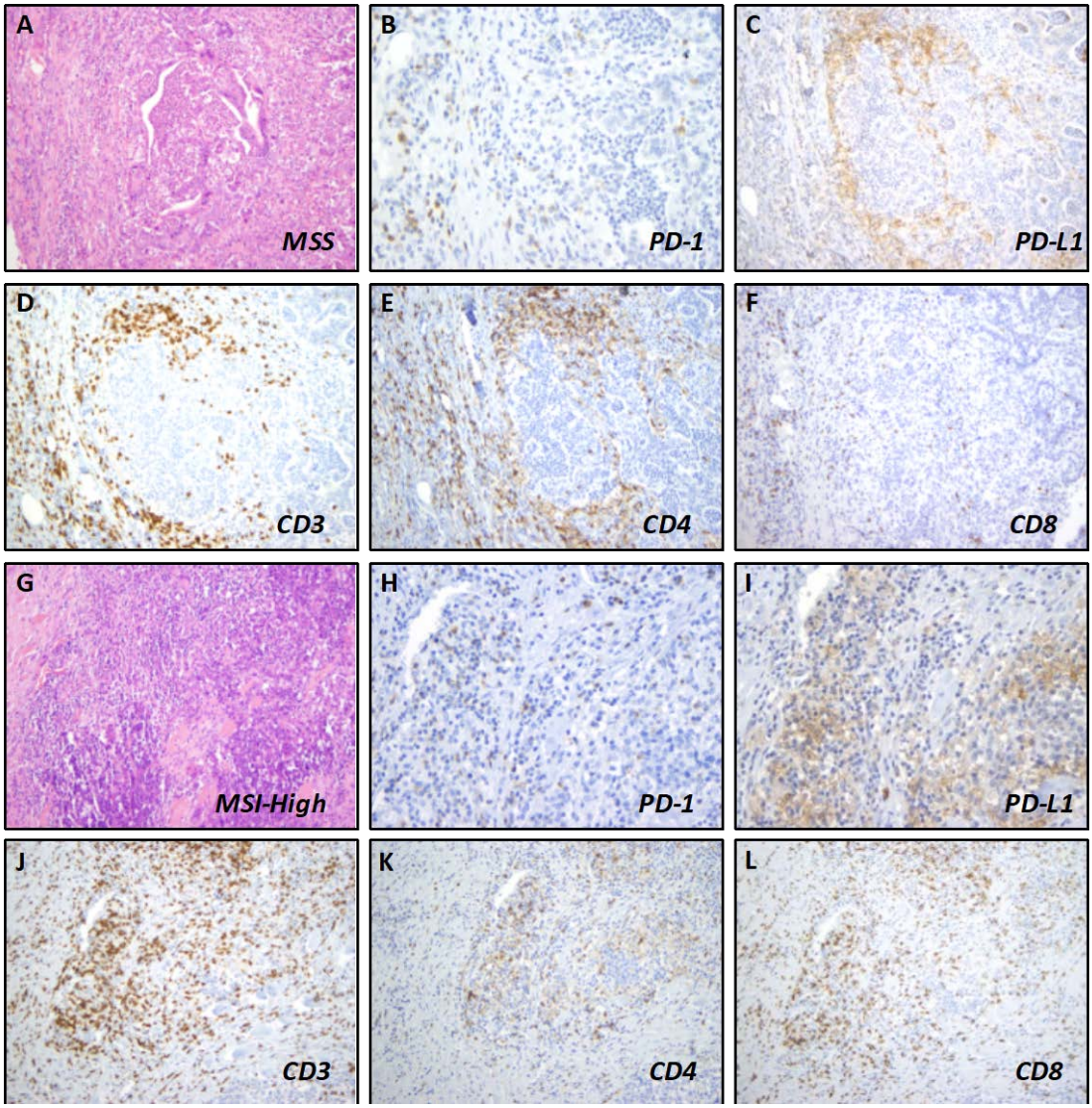

Figure 1. Small intestinal carcinomas express PD-L1 and have high lymphocyte infiltration. **(A-F)** Microsatellite stable (MSS) carcinoma and **(G-L)** Microsatellite instability (MSI)-high medullary carcinoma: **(A, G)** H&E and IHC staining of **(B, H)** PD-1, **(C, I)** PD-L1, **(D, J)** CD3, **(E, K)** CD4 and **(F, L)** CD8 positive cells. All images are 10x with the exception of PD-1 which is 20x.

Table 1. PD-L1 positive tumors have a higher lymphocyte infiltrate.

# of immune cells (per hpf)**	PD-L1 IHC		P value
	Positive* (n=12)	Negative (n=14)	
CD3+	433 ± 22	239 ± 31	< 0.01
CD4+	283 ± 21	185 ± 24	< 0.01
CD8+	151 ± 31	54 ± 15	< 0.01

* Tumors were considered PD-L1 positive if >5% of tumor cells or inflammatory cells stained with an anti-PD-L1 antibody; ** hpf, high-powered field.

There is a strong correlation between non-synonymous mutation burden and response to anti PD-1 therapy in non-small cell lung cancer (NSCLC).[37] About 15% of sporadic colorectal cancers (CRC) have defects in the DNA mismatch repair (MMR) pathway which leads to a high frequency of somatic alterations compared to tumors with intact MMR.[38] Our preliminary data estimated that 27% (7/26) of small bowel adenocarcinomas are microsatellite instability (MSI)-high, consistent with a study reporting 24% of small bowel adenocarcinomas (n=37) with MSI-high status.[39] In a phase II study evaluating the clinical activity of pembrolizumab (anti-PD1) in patients with progressive metastatic carcinoma with or without MMR deficiency, the objective response rate and immune-related progression-free survival rate were 40% and 78% respectively for MMR-deficient colorectal cancer (CRC) and 0% and 11% for MMR-proficient CRC.[40]

Table 2. MSI-high tumors are more likely to express PD-L1.

MSI status	PD-L1 IHC		Total
	Positive*	Negative	
MSS**	5 (26%)	14 (74%)	19
MSI-high	7 (100%)	0 (0%)	7
Total	12 (46%)	14 (54%)	26

* Tumors were considered PD-L1 positive if >5% of tumor cells or inflammatory cells stained with an anti-PD-L1 antibody. ** MSS, microsatellite stable.

Patients with MMR-deficient CRC had responses similar to patients with MMR-deficient non-CRC, including two patients with MMR-deficient small bowel adenocarcinoma (SBA). In our study of 26 small intestinal adenocarcinomas, we noted that 100% (n=7) of MSI high tumors expressed PD-L1 (**Table 2** and **Figure 1**). Based on these data, we hypothesize that MSI high SBA will have a better response to PD-L1 inhibition than MSS small bowel adenocarcinoma due to a higher non-synonymous coding mutation burden. We propose to examine MSI status in SBA in patients, where testing has not been performed in the clinic, by utilizing the MSI Analysis System (Promega) or by IHC analysis of MLH1, MSH2, MSH6, and PMS2, when DNA is not available. Furthermore, we will determine non-synonymous mutation burden in SBA (n=25) by exome sequencing (PE-100; 100x coverage; Illumina HiSeq300) of fresh-frozen, pre-treatment tumor biopsies and matched patient blood. In addition to generating data regarding mutation burden, exome sequencing may uncover novel driver mutations since neither exome nor whole genome sequencing has been previously reported in this rare disease. In addition to or alternative to exome sequencing, other genetic

testing may also be performed on the tumor specimens if new clinical or pre-clinical data emerge that unveil novel genomic biomarkers of response.

4.4. Avelumab

Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 with high affinity (0.7 nM) and blocks the interaction between PD-L1 and its receptor PD-1. This removes the suppressive effects of PD-L1 on anti-tumor $CD8^+$ T cells, resulting in the restoration of a cytotoxic T cell response. The in vitro study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN-γ) production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1.

The antitumor activity of avelumab has been investigated in various murine tumor models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumor $CD8^+$ T cell responses.

During development, to circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1 and, as consequence, all of the nonclinical studies were conducted in syngeneic murine tumor models in which the immune system of the host is fully intact. It was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores antitumor $CD8^+$ T cell responses, which results in an anti-tumor activity.

Avelumab has demonstrated significant nonclinical activity as a monotherapy and in various combination therapy settings. In general, the anti-tumor immunotherapy via blockade of the PD-1/PD-L1 axis seems not to be limited to any specific tumor types, but there is recent evidence that PD-L1 tumor expression is a pre-requisite to achieving an objective response upon blockade of the PD-1/PD-L1 axis.[41] The clinical relevance of PD-1/PD-L1 blockade has been demonstrated in Phase I trials performed with antibodies targeting either PD-L1 or PD-1.[41,42]

Given the important role of PD-L1 in the suppression of T-cell responses, and the mode of action of avelumab which blocks the interaction between PD-L1 and its receptors, avelumab is being developed as a potential therapy for subjects with various tumors.

Clinical Phase I/II trials with monoclonal antibodies targeting either PD-L1 or PD-1 have shown promising hints for clinical efficacy, for example objective tumor response in indications such as NSCLC, melanoma, and ovarian cancer.[41-43]

Avelumab has two main mechanisms of action for exerting anti-tumor effects:

1. PD-L1 ligand on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, using an anti-PD-L1 antibody to block the PD-L1 ligand's interaction with PD-1 or B7-1, can release T cells from immunosuppression and lead to elimination of tumor cells by T cell
2. Compared with normal tissues, tumor cells may express high levels of PD-L1 on their surface. As a fully human IgG1 monoclonal antibody, avelumab has potential for antibody-dependent cellular cytotoxicity (ADCC). Upon binding to PD-L1 on tumor cells, and binding

of Fc antibody portions to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

Therefore, blocking PD-L1 inhibitory mechanisms by interactions not only with PD-1 but also the other ligand, B7-1, avelumab offers unique therapeutic potential compared with monoclonal antibodies targeting PD-1.

4.5. Clinical Experience with Avelumab: Safety and Preliminary Efficacy

Avelumab is currently in development by Merck KGaA, Darmstadt, Germany (within the USA, by EMD Serono, the biopharmaceutical division of Merck KGaA) and Pfizer, and has not been approved for market in any country.

Over 800 patients have received avelumab monotherapy under the JAVELIN clinical trial program as part of at least 3 different clinical trials in solid tumors, including:

- EMR 100070-001 (NCT01772004):
  A Phase I, Open-label, Multiple-ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of Avelumab (MSB0010718C) in Subjects With Metastatic or Locally Advanced Solid Tumors and Expansion to Selected Indications.

- EMR 100070-002 (NCT01943461):
  A Phase I Trial to Investigate the Tolerability, Safety, Pharmacokinetics, Biological and Clinical Activity of Avelumab (MSB0010718C) in Japanese Subjects With Metastatic or Locally Advanced Solid Tumors, With Expansion Part in Asian Subjects With Gastric Cancer.

- EMR 100070-003 (NCT02155647):
  A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects With Merkel Cell Carcinoma.

The primary objective of the global Phase 1 trial (EMR 100070-001) was to determine the maximum tolerated dose (MTD) of avelumab by monitoring dose-limiting toxicities (DLTs). The DLT evaluation period referred to the first 3 weeks after trial treatment during the dose escalation phase following a classical 3 + 3 design.

During dose escalation, none of the subjects treated with doses up to 10 mg/kg experienced a dose limiting toxicity (DLT). Out of the 6 subjects who received 20 mg/kg dose of avelumab, 1 DLT was observed. Occurring 18 days after receiving the first dose of 20 mg/kg avelumab, the DLT event was a Grade 3 immune-related disorder with creatine kinase (CK) increase, myositis, and myocarditis, considered related to trial drug by the investigator. All patients treated at 10 mg/kg had a median trough concentration >1 μg/mL, the necessary concentration for >95% target occupancy (TO).

On the basis of safety, pharmacokinetic (PK), pharmacodyamic (PD), and receptor target occupancy (TO) observations, a dose of 10 mg/kg once every 2 weeks was determined for subsequent expansion involving 16 tumor treatment cohorts.

As of 15 July 2015 (based on data cutoff 01 June 2015), 53 subjects in dose escalation had received avelumab (4, 13, 15, and 21 subjects respectively received 1.0, 3.0, 10.0, and 20.0 mg/kg of

avelumab), and 717 subjects in the pooled expansion part had received 10 mg/kg avelumab with follow-up for at least 4 weeks.

Safety summary data from 717 subjects treated in the pooled treatment expansion cohorts includes a summary of subjects treated in the NSCLC, gastric cancer, ovarian cancer, and urothelial carcinoma expansion cohorts (184, 120, 75, and 44 subjects, respectively).

Treatment-related treatment emergent adverse events (TEAEs) were observed in 498 (69.5%) subjects in the pooled expansion cohort. The most frequently observed treatment-related TEAEs (with an incidence of $\geq$ 2%) of any grade in the pooled expansion cohort were infusion-related reaction (18.7%), fatigue (18.1%), nausea (10.3%), diarrhea (6.8%), chills (6.7%), and decreased appetite (5.2%). Other frequently seen treatment-related TEAEs with an incidence < 5% but $\geq$ 2% included arthralgia, pyrexia, hypothyroidism, pruritus, vomiting, influenza-like illness, rash, anemia, AST increased, myalgia, asthenia, headache, ALT increased, dyspnea, and constipation.

Grade $\geq$ 3 treatment-related TEAEs were observed in 77 subjects (10.7%) in the pooled expansion cohort, of which 13.0%, 9.2%, 6.7%, and 4.5% occurred in the NSCLC, gastric cancer, ovarian cancer, and urothelial carcinoma expansion cohorts, respectively.

The most frequently observed Grade $\geq$ 3 treatment-related TEAEs in the pooled expansion cohort were gamma-glutamyltransferase increased, infusion-related reaction, and lipase increased (each occurred in 7 subjects; 1.0%), followed by anemia (6 subjects; 0.8%), fatigue (5 subjects; 0.7%), and AST increased and autoimmune hepatitis (each occurred in 4 subjects; 0.6%). Other Grade $\geq$ 3 treatment-related TEAEs that were observed in $\geq$ 2 subjects included ALT increased, lymphocyte count decreased, and pneumonitis (each in 3 subjects; 0.4%), and asthenia, blood alkaline phosphatase increased, blood creatine phosphokinase increased, colitis, constipation, dyspnea, hyperglycemia, hypokalemia, hypoxia, myositis, and platelet count decreased (each in 2 subjects; 0.3%).

Of the 77 subjects (10.7%) who experienced Grade $\geq$ 3 treatment-related TEAEs, 60 (8.4%) had Grade 3 events, and 14 (2.0%) and 4 (0.6%) reported Grade 4 and Grade 5 treatment-related TEAEs, respectively.

The 14 subjects reporting Grade 4 treatment-related TEAEs included 7 subjects (3.8%) in the NSCLC expansion cohort with the preferred terms (PTs) of infusion-related reaction (2 subjects), amylase increased, embolic stroke, frontal lobe epilepsy, monoplegia, syncope, dyspnea, pneumonitis, and autoimmune neutropenia (each in 1 subject). Further Grade 4 treatment-related TEAEs were seen in 5 subjects of the metastatic breast cancer (MBC) expansion cohort (3.0%) with the PTs of gamma-glutamyltransferase increased, hypokalemia, respiratory failure, anemia, neutropenia, thrombocytopenia, and cardiac arrest (each in 1 subject). The other 2 subjects who reported Grade 4 treatment-related TEAEs were 1 subject in the mesothelioma expansion cohort (blood creatine phosphokinase increased) and 1 subject in the urothelial carcinoma expansion cohort (myositis).

The 4 subjects who experienced Grade 5 treatment-related TEAEs were 2 subjects in the NSCLC expansion cohort (radiation pneumonitis and acute respiratory failure) and 2 subjects in the MBC expansion cohort (respiratory distress and acute hepatic failure).

Preliminary efficacy results of the 184 subjects treated with 10 mg/kg of avelumab once every 2 weeks in the NSCLC treatment expansion cohort of Phase I Trial EMR 100070-001 with a minimum follow-up of at least 6 months as of 15 January 2015, are available. The objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (including confirmed and unconfirmed responses) among the 184 NSCLC subjects treated at 10 mg/kg of avelumab was 13.6%, which includes one complete response (CR) (0.5%) and 24 partial responses (PR) (13.0%). In 19 of the 25 responders (with either a CR or PR) (76.0%), the responses were ongoing at the time of the data cutoff. The ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in the pre-planned interim analysis on the expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects).

In the NSCLC expansion cohort, the clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status. An objective response was observed in 19 of 122 subjects (15.6%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median progression free survival (PFS) (12.0 vs 5.9 weeks) and overall survival (OS) (8.9 vs 4.6 months) were both observed in PD-L1 positive compared to PD-L1 negative subjects.

5. PARTICIPANT SELECTION

5.1. Allocation of Slots to Study Sites

This is an investigator-initiated trial with intended single-site enrollment limited to patients enrolling at Vanderbilt University.

5.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Signed and dated written informed consent.

2. Male or female ≥ 18 years of age.

3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

4. Histologically confirmed adenocarcinoma of the small intestine that is advanced (not amenable to surgery) or metastatic (clinical stage IV). For the purposes of this study, ampullary tumors are considered a part of the duodenum and are classified as adenocarcinomas of the small intestine.

5. At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria (Appendix 1) that has not been previously irradiated and which can be followed by CT or MRI.

6. Adequate organ function including:

- Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
- Platelets ≥ 100 × 10^9/L
- Hemoglobin ≥ 9/g/dL (may have been transfused)
- Total serum bilirubin ≤ 1.5 times upper limit of normal (ULN)
- Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 2.5 × ULN (or ≤ 5 × ULN if liver metastases are present)
- Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault (CG) equation (Appendix 3).

7. Archival tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site judged reasonably available prior to initiating treatment, or willingness to undergo fresh pre-treatment tumor biopsy. (Prior to initiating treatment, the screening team must have documentation that an archival or fresh tumor specimen has been requested from a local or outside facility. However, physical possession of requested tissue or waiting for histological analysis or confirmation that an acquired specimen contains tumor tissue sufficient for analysis is not a requirement prior to initiating treatment.) If no archival tissue is available and patient consents to a fresh biopsy, but the patient's lesion is deemed inaccessible to safe biopsy, the patient will be allowed to enroll if otherwise eligible.

8. Female patients of childbearing potential and male patients able to father children who have female partners of childbearing potential must agree to use one highly effective method (defined as less than 1% failure rate per year) and one additional effective method of contraception (Appendix 4) from 15 days prior to first trial treatment administration until at least 30 days after study participant's final dose of avelumab. Females of childbearing potential are defined as those who are not surgically sterile or post-menopausal (i.e. patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months without an alternative medical cause). Post-menopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women.

   Male patients able to father children are defined as those who are not surgically sterile (i.e. patient has not had a vasectomy).

9. Serum pregnancy test (for females of childbearing potential) negative at screening.

10. Re-enrollment of a subject that has discontinued the study as a pre-treatment screen failure (i.e. a consented patient who did not receive avelumab) is permitted. If re-enrolled, the subject must be re-consented. Only the screening procedures performed outside of protocol-specified timing must be repeated.

5.3. Exclusion Criteria

Patients will be ineligible for enrollment into the study if they meet any of the following criteria:

1. There is no restriction on the number of prior therapies. However, prior therapy with antibody or drug specifically targeting T cell regulatory proteins, including but not limited to the following is not allowed: Prior immunotherapy with IL-2 or IFN-α, or an anti-PD-1

(including nivolumab), anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

2. Within 28 days before first dose of avelumab:
   Anti-cancer treatment, major surgery requiring general anesthesia, or the use of any investigational agent.

3. Within 14 days before first dose of avelumab:
   Therapeutic or palliative radiation therapy. (Subjects receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days before the first dose of avelumab.)

4. Current use of immunosuppressive medication, except the following:
   - Subjects are permitted the use of corticosteroids with minimal systemic absorption (e.g. topical, intra-articular, intranasal, and inhaled);
   - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent are permitted;
   - A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. CT scan premedication against contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

5. Previous malignant disease other than adenocarcinoma of the small intestine within the last 5 years, with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ considered curatively treated (i.e. complete remission achieved at least 2 years prior to first dose of avelumab AND additional therapy not required while receiving study treatment).

6. All subjects with brain metastases, expect those meeting the following criteria:
   - Brain metastases that have been treated locally and are clinically stable for at least 2 weeks prior to enrollment
   - No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable.
   - Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent)

7. Receipt of any organ transplantation including allogeneic stem-cell transplantation.

8. Significant acute or chronic infections requiring systemic therapy.

9. Known history of testing positive for human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS).

10. Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).

11. Active autoimmune disease with reasonable possibility of clinically significant deterioration when receiving an immuno-stimulatory agent. Subjects with Type 1 diabetes mellitus, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

12. Interstitial lung disease that is symptomatic or which may interfere with the detection or management of suspected drug-related pulmonary toxicity.

13. Uncontrolled asthma [defined as having 3 or more of the following features of partially controlled asthma within 28 days prior to starting study treatment: Daytime symptoms more than twice per week, any limitation of activities, any nocturnal symptoms/awaking, need for reliever/rescue inhaler more than twice per week, or known lung function (PEF or FEV1) without administration of a bronchodilator that is < 80% predicted or personal best (if known)].

14. Current symptomatic congestive heart failure (New York Heart Association ≥ class II), unstable cardiac arrhythmia requiring therapy (e.g. medication or pacemaker), unstable angina (e.g. new, worsening or persistent chest discomfort), or uncontrolled hypertension (systolic > 160 mmHg or diastolic > 100mmHg). Or any of the following occurring within 6 months (180 days) prior to first dose of avelumab: Myocardial infarction, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack, or serious cardiac arrhythmia requiring medication. (Use of antihypertensive medication to control blood pressure is allowed.)

15. Concurrent treatment with a non-permitted drug (see Section 10).

16. Requirement of anticoagulant therapy with oral vitamin K antagonists such as Coumadin (warfarin). Low-dose anticoagulants for the maintenance of patency in a central venous access device or the prevention of deep vein thrombosis or pulmonary embolism is allowed. Therapeutic use of low molecular weight heparin is allowed.

17. Persisting toxicity related to prior therapy that has not reduced to Grade 1 [National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03]; however, alopecia and sensory neuropathy Grade ≤ 2 is acceptable.

18. Known severe (Grade ≥ 3 NCI-CTCAE v4.03) hypersensitivity reactions to monoclonal antibodies, including hypersensitivity to the investigational agent or any component in its formulations, or history of anaphylaxis.

19. Vaccination within 28 days of the first dose of avelumab and while on trial is prohibited, except for administration of inactivated vaccines (for example, inactivated influenza vaccine).

20. Pregnant or breastfeeding females.

21. Known alcohol or drug abuse

22. Prisoners or subjects who are involuntarily incarcerated.

23. Other severe acute or chronic medical condition, including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis, or psychiatric condition 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.

5.4. Inclusion of Underrepresented Populations

Women and men of all races and ethnic groups are eligible for this trial. There is no bias towards gender, age, or race in the clinical trial outlined.

5.5. Number of Patients and Replacement of Patients Who Discontinue Early

Approximately 25 patients evaluable for response are anticipated to enroll in this study at Vanderbilt University Medical Center.

In general, it intended that patients will be treated until disease progression or intolerable toxicity. The criteria for patient discontinuation are listed in Sections 9 and 11.

If a patient discontinues study treatment for reasons clearly not related to study treatment, after completing fewer than one planned infusion of avelumab, and/or receiving <75% of the total intended dose of avelumab over the first cycle of treatment + an additional 14 days (i.e. first 28 days after initiating patient's first dose of avelumab), then that patient will be considered not evaluable for response to study treatment and may be replaced with a new patient.

6. REGISTRATION PROCEDURES

6.1. Registration

All patients MUST be registered with the VICC prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Central Standard Time Monday through Friday.

1) All sites must email the VICC CTSR Coordinating Center at Coordinating.Center@Vanderbilt.edu to notify of upcoming registration and ensure slot availability. The following information should be included in your email:

    - Study number
    - Patient initials
    - Disease type
    - Anticipated consent date

- Anticipated start date

2) Email the following documents to the Coordinating Center for eligibility review and patient enrollment (**coordinating.center@vanderbilt.edu**):
    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - Patient Enrollment Form
    - Eligibility supporting documents such as pathology reports, laboratory tests, etc. *or* EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
    - Signed and completed Eligibility Checklist. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: All study documents should be received 24-48 hours prior to the patient's anticipated start date. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center. Please email the Coordinating Center if enrollment is needed sooner.

Upon satisfactory review of eligibility documents submitted, the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned Clinical Research Associate (CRA) once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to investigational treatment. Following registration, eligible participants should begin study treatment consistent with the protocol no later than 28 days after registration/enrollment by the VICC Coordinating Center. If a participant does not receive protocol therapy following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact should be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Coordinating Center will require a new, signed Informed Consent document.
Issues that would cause treatment delays should be discussed with the Protocol Chair.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

7. SCHEDULE of ASSESSMENTS

7.1. Study Calendar

Protocol Activities	Screening *≤ 28 Days Prior to First Dose*	Day 1 of Cycles ≥ 1 *Every 14 days (+3 days)*[11]	Post Treatment	
			EOT/ Withdrawal[14]	Follow-Up[17]
Clinical Assessments				
Consent, Medical History & Demographics	X			
Physical Examination and ECOG	X	X[9]	X	X[16]
Vital Signs[1]	X	X[1]	X	X[16]
Con Meds & Adverse Events	X	X[9]	X	X[16]
Height and Weight[2]	X	X[2]	X	
Survival Follow-up				X[18]
Laboratory Studies				
Hematology and Blood Chemistry[3]	X	X[10]	X	X[16]
HCV and HBV Testing	X			
Serum Pregnancy Test[4]	X	X[4]	X	
Free T4 and Thyroid Stimulating Hormone (TSH)	X	X[5]	X	X[5]
Tumor and Pharmacogenetic Assessments				
CT or MRI Scans[6]	X[6]	X[6]	X[15]	X[19]
Archival Tumor Tissue	X[7]			
Fresh Tumor Biopsy	X[8]			
Pharmacogenetic Blood Sample		X[11]		
Treatment				
Avelumab infusion (10 mg/kg)		X[12,13]		

Notes:

1. Vital signs to include heart rate, blood pressure and temperature (oral or tympanic). On days of each avelumab treatment: Pre-Dose and Post-Dose vitals should respectively be recorded ≤ 10 minutes prior to the start of the avelumab infusion (Pre), and ≤ 10 min after the end of the avelumab infusion (EOI). Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.
2. Height only at baseline. Weight within 3 days prior to every dose of avelumab. As per Note 11 below and protocol Section 8.2, avelumab dose must be adjusted if patient's weight changes ± 10%.
3. Hematology to include: White blood count (WBC) with differential; hemoglobin, hematocrit and platelet count. Blood chemistry to include: Sodium, potassium, calcium, chloride, and bicarbonate; BUN, serum creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, total protein, and albumin.
4. Serum pregnancy test required for females of childbearing potential, during Screening and on Cycle 1, Day 1 (unless already done within 72 hours prior to first dose of avelumab). Subsequent serum pregnancy tests to be done every 4 weeks on Day 1 of each cycle and at End of Treatment. Females of childbearing potential are defined as those not surgically sterile or not post-menopausal (i.e. patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months without an alternative medical cause). Postmenopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women (if a patient's postmenopausal status is considered for childbearing potential and study required contraception).

5. Free T4 and TSH levels will be tested at screening, Cycle 3 Day 1, and then every 8 weeks while patients are on therapy. Free T4 and TSH levels will also be tested at EOT or at the Follow-up visit (if not performed in the previous 8 weeks.
6. Baseline evaluation of disease status by CT or MRI within 28 days prior to first dose of avelumab. Baseline and subsequent scans to include imaging of the chest, abdomen and pelvis. The first scheduled re-scan should be performed and evaluated 7 to 8 weeks after Cycle 1, Day 1 treatment, with subsequent scheduled scans intended every 8 to 9 weeks thereafter irrespective of dose delays. Thus, the first re-scan is anticipated during Week 2 of Cycle 4 (with evaluation prior to dosing on Cycle 5, Day 1). Additional re-scanning is anticipated during Week 2 of every 4th cycle (i.e. Week 2 of Cycles 8, 12, 16, etc) prior to infusion in the subsequent cycle (i.e. re-scanning prior to Day 1 of Cycles 5, 9, 13, 17, etc). Scanning on the same day as dosing is discouraged but allowed, provided scan results receive appropriate evaluation prior to study treatment (e.g. first re-scan is permitted on Cycle 5, Day 1, prior to treatment later that same day). Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician.
7. Archival tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site judged reasonably available prior to initiating treatment, or willingness to undergo fresh pre-treatment tumor biopsy. Prior to initiating treatment, the screening team must have documentation that a paraffin block(s), unstained slides from a paraffin block(s), or a fresh biopsy has been requested from a local or outside facility. (However, physical possession of requested tissue, or waiting for histological analysis or confirmation that a certain number of acquired specimen slides are known to contain tumor tissue, is not a requirement prior to initiating treatment.) Please note: Archival or fresh biopsy should be excisional, incisional or core needle; fine needle aspiration is not sufficient. Patients without available or sufficient archival tumor samples (if otherwise eligible) will be allowed to participate, if they are willing to have a fresh biopsy of a primary or metastatic lesion. If no archival tissue is available and patient consents to a fresh biopsy, but the patient's lesion is deemed inaccessible to safe biopsy, the patient will be allowed to enroll if otherwise eligible.
8. In addition to the mandatory archival tissue or fresh tissue, an optional fresh biopsy will be requested from consenting subjects (including those with pre-existing archival tissue) with primary or metastatic lesion judged amenable to medically safe excisional, incisional or core needle biopsy.
9. On Cycle 1, Day 1: Physical exam (including ECOG performance status) and review of Con Meds and Adverse Events not required if already completed within 7 days prior to first dose of avelumab. After initiation of Cycle 4, physical exams may be performed monthly (i.e. after Cycle 4, Day 1 exam to confirm satisfactory completion of Cycle 3, the next regularly scheduled physical exam may occur 4 weeks later, on Cycle 6, Day 1; with subsequent monthly physical exams intended every even cycle, on Day 1 of Cycles 8, 10, 12, etc).
10. Hematology and blood chemistry must be collected prior to each avelumab dose, at the end of treatment visit, and at 30 days post-treatment safety follow-up.
11. Pharmacogenetic (PG) blood obtained once, prior to patient's first avelumab dose on Cycle 1, Day 1.
12. The avelumab dose will be 10 mg/kg administered as 1-hour intravenous (IV) infusion every 2 weeks (Q2W). Every effort should be made to target infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps, time windows of -10 minutes and +20 minutes is permitted (i.e. scheduled avelumab infusion time is 60 minutes: -10 min/+20 min). See protocol Section 9 for recommended infusion pre-medications. Avelumab dosing will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to each avelumab dose. If a weight loss or gain ≥ 10% is observed (compared to the weight used to calculate the immediately prior dose), then the amount of avelumab required for a current dose must be recalculated using the most recent weight obtained. Reduction of avelumab dose for toxicity management is not permitted, however avelumab administration may be held due to adverse events, as described in protocol Section 11.
13. Cycle 2, Day 1 dosing should occur 14 days after Cycle 1, Day 1. In the absence of delayed dosing (e.g. due to an adverse event), every reasonable effort should be made to remain on a consistent schedule of 14-day cycles; but for purpose of accommodating holidays, scheduling limitations, etc, subsequent cycles (i.e. Cycles 3+) may occur up to every 14 days +3 days. Consecutive doses of avelumab must be

separated by no fewer than 14 days and, in the absence of adverse event management, no more than 17 days.

14. Reasonable effort should be made to complete End-of-Treatment / Withdrawal procedures on the day it is decided that a patient will no longer receive study treatment. These procedures must be completed subsequent to and not later than 21 days after a patient's final treatment with avelumab (and prior to any subsequent anti-cancer therapy).
15. Unless already done within previous 28 days.
16. A 1-month follow-up clinic visit is intended 28 days (±7 days) after the preceding End-of-Treatment visit (at least 30 days after patient's final treatment with avelumab). Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.
17. Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days (+3 days) after the last dose of avelumab administration. The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a clinic visit or telephone call with a subsequent site visit requested in case any concerns noted during the telephone call.
18. Each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with avelumab until death, end of the study, or until patient withdraws consent, whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.
19. If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans of the chest, abdomen and pelvis should be continued every 8-9 weeks until disease progression is confirmed by imaging.

7.2. Screening Visit Assessments

Prior to performing any study-based procedures, patient informed consent must be obtained.

The following procedures must be completed ≤ 28 days prior to a patient's first dose of study treatment:

- Signed Informed Consent Form
- Medical history and Demographics
- Physical exam
- Vital signs: heart rate, blood pressure and temperature (oral or tympanic)
- Height
- Weight
- ECOG Performance Status
- Concomitant medications (taken up to 28 days prior to Day 1) and Adverse Events
- Complete Blood Count (CBC) with differential
- Serum chemistry, including Free T4 and thyroid stimulating hormone (TSH)
- Serum Pregnancy test in women of childbearing potential (as defined in Sections 7.1 and 8.6)
- Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) testing
- Extent of disease evaluation (by CT or MRI scan of the chest, abdomen and pelvis), within 28 days of study treatment
- Archival tumor tissue requested and/or fresh biopsy of lesion amenable to safe biopsy (see Sections 7.1 and 8.7 for additional detail).

7.3. Cycle 1, Day 1 Assessments

On Cycle 1, Day 1, the following procedures must be completed:

- CBC
- Serum chemistry
- Serum Pregnancy test in women of childbearing potential, unless previously completed ≤ 72 hours prior to a patient's first dose of study treatment
- Weight.

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 7 days prior to a patient's first dose of study treatment:

- Physical Exam (including ECOG performance status) and review of Con Meds and Adverse Events).

On Cycle 1, Day 1, the following procedures will be completed:

- Pharmacogenetic Blood Sample (pre-dose)
- Vital signs (heart rate, blood pressure, and oral or tympanic temperature):
  Pre-Dose: ≤ 10 minutes prior to the start of the avelumab infusion
  Post-Dose: ≤ 10 min after the end
- Avelumab infusion.
- Patients must be observed for 30 minutes post infusion for potential infusion related reactions.

7.4. Additional Cycles Assessments

For patients that continue beyond Cycle 1, the following assessments will occur at the specified weeks:

Week 1 of Each Cycle (e.g. Cycle ≥2, Day 1)

- Physical exam: After initiation of Cycle 4, physical exams may be performed monthly. (After Cycle 4, Day 1 exam to confirm satisfactory completion of Cycle 3, the next regularly scheduled physical exam may occur 4 weeks later, on Cycle 6, Day 1; with subsequent monthly physical exams intended every even cycle, on Day 1 of Cycles 8, 10, 12, etc).
- Vital signs (heart rate, blood pressure, and oral or tympanic temperature):
  Pre-Dose: ≤ 10 minutes prior to the start of the avelumab infusion
  Post-Dose: ≤ 10 min after the end of the avelumab infusion
- Serum Pregnancy test in women of childbearing potential: must be performed every 4 weeks
- Weight (within 3 days prior to every dose of avelumab)
- ECOG Performance Status
- Concomitant Medications and Adverse Events
- CBC and Serum chemistry: must be performed prior to each avelumab treatment
- Free T4 and thyroid stimulating hormone (TSH) on Day 1 of every odd cycle (every 8 weeks)
- Avelumab infusion.
- Patients must be observed for 30 minutes post infusion for potential infusion related reactions.

Week 2 of every 4th cycle (i.e. Week 2 of Cycles 4, 8, 12, 16, etc)

- Extent of disease evaluation (as per Section 7.1)

7.5. End-of-Treatment / Withdrawal Assessments

Reasonable effort should be made to complete End-of-Treatment / Withdrawal procedures on the day it is decided that a patient will no longer receive study treatment.

The following procedures must be completed not later than 21 days after a patient's final treatment with avelumab (and prior to any subsequent anti-cancer therapy):

- Physical exam
- Vital signs (heart rate, blood pressure, and oral or tympanic temperature)
- Weight
- ECOG Performance Status
- Concomitant Medications and Adverse Events
- CBC
- Serum chemistry, including Free T4 and thyroid stimulating hormone (TSH)
- Serum Pregnancy test (in women of childbearing potential)
- Extent of disease evaluation (if not already performed within the last 28 days).

7.6. Follow-Up Visit Assessments (30-Day and 90-Day)

A 1-month follow-up clinic visit is intended 28 days (±7 days) after the preceding End-of-Treatment visit. Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.

Documented attempts should be made to have patients return to the clinic 28 days (±7 days) after the prior End-of-Treatment visit (at least 30 days after patient's final treatment with avelumab), in order to undergo the following assessments:

- Physical exam
- ECOG Performance Status
- Concomitant Medications and Adverse Events
- CBC and Serum chemistry
- Free T4 and Thyroid stimulating hormone (TSH) if not performed in the previous 8 weeks.

If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans of the chest, abdomen and pelvis should be continued every 8-9 weeks until disease progression is confirmed by imaging.

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days (+3 days) after the last dose of avelumab administration.
The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

7.7. Survival Follow-Up

Each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with avelumab until death, end of the study, or until patient withdraws consent, whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

8. STUDY PROCEDURES

8.1. Medical History

A medical history will include all relevant prior medical conditions, surgeries or other medical procedures.

8.2. Physical Examination

Physical examination: The physical examination should include an examination of major body systems, ECOG performance status, body weight, height (at Screening Visit only), vital signs (temperature, blood pressure, pulse rate).

All patients should be weighed within 3 days prior to each avelumab dose.

If a weight loss or gain ≥ 10% is observed (compared to the weight used to calculate the immediately prior dose), then the amount of avelumab required for a current dose must be recalculated using the most recent weight obtained.

8.3. Extent of Disease Assessment

Tumor response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, to establish disease progression by CT or MRI. In addition, other radiographic or scintigraphic procedures (such as radionuclide bone scans), as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement. The same method of assessment should be used throughout the study. Investigators should select target and non-target lesions in accordance with RECIST v1.1 guidelines. Follow-up measurements and overall response should also be in accordance with these guidelines. To be assigned a status of confirmed PR or CR, changes in tumor measurements should be confirmed by repeated assessments that should be performed ≥30 days after the criteria for response are first met.

The extent of disease assessment should be completed until it has been determined the patient has progressive disease (in accordance with RECIST v1.1). In the event the patient discontinues study treatment for reasons other than disease progression, an extent of disease assessment should be completed as soon as possible relative to the date of study termination to ensure disease progression is not present and to assess overall disease status. In such patients, this assessment should occur no later than 28 days after a patient's last treatment with avelumab (and prior to any subsequent anti-cancer therapy).

8.4. Complete Blood Count

A complete blood count (CBC) will include a white blood count (WBC) with differential, hemoglobin, hematocrit and platelet count.

8.5. Blood Chemistry

Blood chemistry will include electrolytes (sodium, potassium, calcium, chloride, and bicarbonate), BUN, serum creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, total protein, and albumin. Thyroid stimulating hormone (TSH) will be drawn during screening and periodically during treatment. See the Schedule of Assessments (Section 7.1) for specific time points.

8.6. Serum Pregnancy Test

A serum pregnancy test will be obtained for all females of childbearing potential, defined as those not surgically sterile or not post-menopausal (i.e. patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 months without an alternative medical cause). Postmenopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women (if a patient's postmenopausal status is considered for childbearing potential and study required contraception).

8.7. Archival and Optional Fresh Tumor Samples

Pre-treatment archival tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site must be judged to be reasonably available prior to initiating treatment, or the patient must be willing to undergo a fresh pre-treatment tumor biopsy. Prior to initiating treatment, the screening team must have documentation that a paraffin block(s), unstained slides from a paraffin block(s), or a fresh biopsy has been requested from a local or outside facility. (However, physical possession of requested tissue, or waiting for histological analysis or confirmation that a certain number of acquired specimen slides are known to contain tumor tissue, is not a requirement prior to initiating treatment.) Please note: Archival or fresh biopsy should be excisional, incisional or core needle; fine needle aspiration is not sufficient.

Patients (including those with pre-existing archival tissue) may elect to have an optional fresh biopsy of a primary or metastatic lesion judged amenable to medically safe excisional, incisional or core needle biopsy.

Archival tumor samples obtained at the time of metastasis are preferred over tumor samples obtained at the time of primary diagnosis. Approximately 50 total microns of tumor sample (i.e. about 10 slides of 5 microns each) is desired for this purpose – see lab manual for additional details.

In cases where both archival and optional fresh tumor biopsy tissue are available, both archival and fresh samples will be requested.

Patients without available or sufficient archival tumor samples (if otherwise eligible) will be allowed to participate, if they are willing to have a fresh biopsy of a primary or metastatic lesion. If no

archival tissue is available and patient consents to a fresh biopsy, but the patient's lesion is deemed inaccessible to safe biopsy, the patient will be allowed to enroll if otherwise eligible.

9. STUDY TREATMENT

9.1. Infusion Premedications

Subjects will receive avelumab by IV infusion following pretreatment with H1 blockers and acetaminophen once every 2 weeks. In order to mitigate infusion-related reactions, premedication with an antihistamine plus paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first four infusions of avelumab is mandatory. For example: 25-50 mg diphenhydramine and 500-650 mg paracetamol (acetaminophen) IV or oral equivalent. Premedication should be administered for subsequent avelumab infusions based upon clinical judgement and presence/severity of prior infusion reactions. As appropriate, this may be modified based on local treatment standards and guidelines provided it does not include systemic corticosteroids.

9.2 Avelumab Infusion

In this clinical trial, the avelumab dose will be 10 mg/kg administered as 1-hour intravenous (IV) infusion every 2 weeks (Q2W). Patient vital signs will be monitored at ≤10 minutes prior to avelumab infusion, and ≤10 minutes after avelumab infusion. Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions. See schedule of assessments (Section 7.1) for the specific vital signs that will be monitored.

This dose is the recommended dose administered to more than 480 patients in the ongoing dose-expansion phase of study EMR 100070-001 (see Section 4 for details).

Avelumab will be administered on Day 1 of each cycle after all assessments and procedures have been completed as described in the Schedule of Assessments table (Section 7).

Cycle 2, Day 1 dosing should occur 14 days after Cycle 1, Day 1. In the absence of delayed dosing (e.g. due to an adverse event), every reasonable effort should be made to remain on a consistent schedule of 14-day cycles; but for purpose of accommodating holidays, scheduling limitations, etc, subsequent cycles (i.e. Cycles 3+) may occur up to every 14 days +3 days. Consecutive doses of avelumab must be separated by no fewer than 14 days and, in the absence of adverse event management, no more than 17 days.

Every effort should be made to target infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps, time windows of -10 minutes and +20 minutes are permitted (i.e. the scheduled avelumab infusion time is 60 minutes: -10 min/+20 min).

The exact duration of infusion should be recorded in both source documents and data case report forms (CRFs). Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 11.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to every dose of avelumab.

If a patient experiences either a weight loss or gain ≥ 10% compared to the weight used to calculate the patient's immediately prior dose, then the amount avelumab required for a current dose must be recalculated using the most recent weight obtained.

Avelumab dose reduction for toxicity management is not permitted, however avelumab administration may be held due to adverse event as described in Section 11.

Even if treatment is held, the numerical 14-Day "cycle clock" should still keep running as scheduled, as an overall indication of time elapsed since the first infusion on Cycle 1, Day 1 (e.g. if treatment is withheld on Cycle 2, Day 1, the respective calendar day will still be recorded as Cycle 2, Day 1 and not Cycle 1, Day 15, etc). In the event of treatment interruption, the study records should reflect treatment was withheld; other visit procedures, including re-scanning for purpose of monitoring for disease progression should still be completed as previously intended by the study calendar.

9.3. Duration of Study Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance to study treatment. In the absence of treatment delays due to adverse event, treatment may continue until applicability of a criterion listed in Sections 9.4 and 11.

9.4. Discontinuation of Study Treatment

Discontinuation of study treatment will be required if deemed by the investigator to be in the subject's best interest or if subject meets any of the criteria for study withdrawal listed below:

- Disease progression as assessed by RECIST 1.1 criteria (Appendix 1), unless the subject meets criteria for treatment beyond progression (Section 9.7);
- Termination of the study by Vanderbilt or relevant regulatory authority;
- Drug availability or study supply discontinued;
- The patient withdraws consent to undergo further treatment;
- The patient is lost to follow-up, refuses further follow-up, or is noncompliant;
- The patient no longer requires treatment (e.g. patients having experienced a tumor reduction followed by resection and no longer with evaluable disease);
- Initiation of treatment with another anti-cancer therapy;
- Additional protocol specified reason for discontinuation (e.g. related to adverse event), see Section 11.

In the case of pregnancy, the investigator must immediately notify the EMD Serono medical designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio warrants continuation of study drug, a discussion between the investigator and appropriate internal and external entities must occur (e.g. the IRB and the EMD Serono medical designee).
If a patient does not return for a scheduled visit, every reasonable effort should be made to contact the patient. In any circumstance, every reasonable effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved treatment-related adverse events.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 7. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (e.g. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).
If study drug is discontinued, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.
If the patient withdraws from the study, and also withdraws consent for disclosure of future information during follow-up, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.5. Duration of Follow-Up

In general, it intended that patients will be treated until disease progression or intolerable toxicity. The criteria for patient discontinuation are listed in Section 9.4. Patients should be assessed when it is decided that the patient will no longer receive study treatment; and assessed again 28 days (± 7 days) later – i.e. at least 30 days after patient's final treatment with avelumab.

Subsequently, each patient will be followed for survival every 3 months (± 14 days) after patient's final treatment with avelumab until death, end of the study, or until patient withdraws consent, whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

9.6. Withdrawal from Study

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, or behavioral reasons; or the inability of the subject to comply with the protocol-required schedule of study visits or procedures, or an inability to maintain voluntary informed consent. Reasons for withdrawal from the study might include: Subject withdraws consent for follow-up, subject is lost to follow-up, or study is terminated for any reason.

9.7. Treatment After Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents such as avelumab may produce antitumor effects by potentiation of endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Subjects treated with avelumab will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease (PD) while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Investigator-assessed clinical benefit and absence of rapid disease progression
- Tolerating study drug

- Stable performance status
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab.

All decisions to continue treatment beyond initial progression should be documented in the study records. The subject will continue to receive monitoring according to the Schedule of Assessments listed in Section 7.

If radiologic imaging shows initial disease progression, repeat scanning and tumor assessment should be performed 4 to 6 weeks later in order to confirm the observation, unless an alternative rescanning interval is provoked by clinical deterioration.

Assigned study treatment may be continued at the investigator's discretion while awaiting radiologic confirmation of disease progression. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target as well as non-target lesions. **For subjects continuing avelumab beyond initial progression, further disease progression is defined as an additional 10% increase in tumor burden volume from time of initial PD.** This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. For subjects with evaluable disease only, further progression is defined as unequivocal disease progression of non-target lesions or the development of new measurable lesions from time of initial PD.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore be included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

Upon documentation of further disease progression, avelumab treatment should be discontinued permanently. However, according to the investigator's clinical judgment and after any necessary discussion between the investigator and EMD Serono, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with avelumab. The investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.

Patients who stop avelumab treatment and then experience radiologic disease progression thereafter will be eligible for re-treatment with avelumab at the discretion of the investigator and after IRB approval and any necessary discussion with EMD Serono if: 1) no anti-cancer treatment was administered since the last dose of avelumab, 2) the patient does not meet the safety withdrawal criteria, and 3) the trial is still open. Patients will resume avelumab therapy at the same dose and schedule applied at the time of discontinuation.
Global deterioration of health status requiring discontinuation of treatment without contemporaneous evidence of objective disease progression should be reported as 'symptomatic

deterioration'. Every effort should be made to document objective progression (i.e. radiographic confirmation) even after discontinuation of treatment.

10. CONCOMITANT TREATMENT

10.1. Supportive Care Guidelines

Patients should be advised to inform their study doctor of all concomitant medications, including over-the-counter medications and dietary supplements.
All concomitant medications taken within 28 days prior to first dose of study drug treatment and during the clinical trial (up to 30 days post-treatment) must be recorded on the appropriate Case Report Form.

Subjects are permitted the use of corticosteroids with minimal systemic absorption (e.g. topical, ocular, intra-articular, intranasal, and inhaled).
Adrenal replacement steroid doses including doses > 10 mg daily prednisone are permitted.

A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Section 11.

- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. Monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed as appropriate.

10.2. Prohibited and/or Restricted Medications and Therapies

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Immunotherapy or immunosuppressive drugs (i.e. chemotherapy or systemic corticosteroids) except for short-term treatment of allergic reactions or for the treatment of an immune-related adverse event (irAE). Short-term administration of systemic steroids (e.g. for allergic reactions or the management of irAEs) is allowed. Topical and inhaled steroids are allowed.

- Systemic corticosteroids > 10 mg daily prednisone equivalent, except as stated in Section 10.1 or to treat a drug-related AE (e.g. Section 11).

- Growth factors (granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor) are prohibited.

- Vaccination within 28 days of the first dose of avelumab and while on study is prohibited, except for administration of inactivated vaccines (for example, inactivated influenza vaccines).

- Bisphosphonate or denosumab treatment is not allowed unless it has been initiated more than 14 days prior to receiving the first administration of avelumab.

- Anti-cancer systemic chemotherapy or biological therapy or investigational agents other than avelumab.

- Surgical resection of tumor.
- Other experimental pharmaceutical products.

- Herbal remedies reasonably known to have immunostimulating properties (e.g. mistletoe extract) or reasonably known to potentially interfere with major organ function (e.g. hypericin).

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

10.3. Clarifications about Steroid Use

Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes.[44,45] Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes.[46]

Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: For treatment of infusion-related reactions and short-term treatment of immune-related adverse events (irAEs), steroids are permitted according to the modalities outlined in Section 11.
- Physiologic use: Adrenal replacement steroid doses including doses > 10 mg daily prednisone or equivalent is acceptable.
- Prophylactic use (e.g. for the prevention of acute infusion-related reactions) is prohibited, *except* prior to CT or MRI scan, or for the management of immune-related adverse events (irAEs) as outlined in Section 11.

10.4. Hematopoietic Growth Factors and Transfusional Support

- Packed red blood cell and platelet transfusions should be administered only if clinically indicated, and should be avoided during the first 28 days after the start of a patient's first avelumab infusion.

- Growth factors (granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor) are prohibited.

Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study (if necessary, then ideally after the first 28 days of study treatment) at the discretion of the treating physician if clinically indicated.

10.5. Concomitant Radiotherapy

The potential for overlapping toxicities with radiotherapy and avelumab is currently unknown. Per eligibility criteria, prior therapeutic or palliative radiation therapy must be completed within 14 days prior to first dose of avelumab. After beginning study treatment, palliative radiotherapy is generally not recommended while receiving avelumab.

However, local radiotherapy of isolated lesions with palliative intent (e.g. bleeding, pain, compression, etc) is permitted if considered medically necessary by the treating physician. The irradiated area should be as small as possible. Irradiated lesions will be followed for disease progression but will not be accounted for in the evaluation of the response.

Subjects requiring palliative radiotherapy should be assessed for disease progression. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should be present at baseline; otherwise, painful lesion(s) requiring radiotherapy should be considered as a sign of disease progression.

Subjects considered as having progressive disease are required to discontinue study therapy, or if appropriate, continue avelumab therapy as treatment beyond progression. Administration of additional avelumab to subjects who experienced disease progression at the time of palliative radiotherapy should follow guidelines specified in Section 9.7 (Treatment After Initial Evidence of Radiologic Disease Progression).

If palliative radiotherapy to bone metastases is required, then avelumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and adverse events considered related to radiotherapy should resolve to Grade ≤ 1 prior to resuming avelumab.

Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy while on study treatment. Details of palliative radiotherapy should be documented in the source records and case report form (CRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events.

11. ADVERSE EVENT MANAGEMENT

11.1. Criteria for Holding Treatment for Adverse Event Possibly Related to Avelumab

No dose *reductions* of avelumab are permitted for the management of adverse events experienced by individual patients in this study.

As outlined below, *treatment delays* of up to 4 weeks (28 days) from last dose of avelumab are allowed.

Avelumab Treatment Should be DELAYED up to 4 Weeks (28 days) for the following Adverse Events if at least Possibly related to Avelumab:

- Any Grade ≥ 3 drug-related adverse event, with the exception of alopecia and the following laboratory exceptions for lymphopenia, leukopenia, AST, ALT, and total bilirubin:
  - Grade 3 lymphopenia or leukopenia do not require a dose delay.
  - If subject had baseline AST, ALT, or total bilirubin within normal limits, then delay dosing for drug-related Grade ≥ 2 liver function toxicity.
  - If subject had baseline AST, ALT, or total bilirubin that was Grade 1, then delay dosing for drug-related Grade ≥ 3 liver function toxicity.
- Any AE, laboratory abnormality, or intercurrent illness regardless of severity or attribution to avelumab which, in the judgment of the investigator, warrants delaying investigational treatment with avelumab.

IMPORTANT:
The above list does NOT include other events which may require holding study treatment – even in cases of severity less than Grade 3 and regardless of attribution to study drug. Events such as Immune-Related Adverse Events (irAEs) of Special Interest, Infusion Reactions, Hypersensitivity, or Tumor Lysis Syndrome (if applicable) should be managed according to local institutional practice.

Dose delay criteria apply for drug-related adverse events – i.e. events which in the investigator's opinion are possibly, probably, or definitely related to avelumab. For adverse events deemed unlikely or unrelated to avelumab (e.g. related to disease), the medical judgement of the investigator should determine the extent to which a treatment delay is appropriate.

If avelumab treatment is delayed for > 4 weeks (28 days) from the last dose of avelumab, the subject must be permanently discontinued from study therapy, except as may be specified in Sections 9.4 and 11.3.

The window for a maximal 4 week (28 day) avelumab treatment delay begins on the calendar day of the most recent avelumab treatment preceding an event in question, and concludes on the calendar day that an immediately subsequent avelumab treatment is initiated.

In the event of multiple toxicities, treatment delay should be based on the worst toxicity observed.

In general, an adverse event related to study treatment that results in a dose delay should be present on the day of intended study treatment (i.e. a delayed toxicity that develops mid-cycle, but which is no longer present or has resolved to an acceptable grade on the day of intended dosing, generally does not require a delay in treatment).

Patients should be instructed to notify their study team at the first occurrence of any adverse symptom. In addition to dose delays according to protocol guidance, investigators are encouraged to employ best supportive care according to local institutional clinical practice.

Even if study drug dosing is interrupted, tumor scans and other visits, assessments and procedures should continue per protocol (i.e. per timeline in place prior to the dose interruption).

11.2. Criteria for Resuming Treatment Held for Adverse Event Related to Avelumab

If a subject's avelumab treatment is held due to an adverse event that is possibly, probably or definitely related to avelumab, the subject may resume treatment with avelumab when the related adverse event resolves to ≤ Grade 1 or to patient's baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue or alopecia of any grade.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with a Grade 2 AST/ALT or total bilirubin may resume treatment IF patient's respective baseline AST/ALT or total bilirubin was Grade 1 and the reason for patient's dose delay was NOT due to a 2 or more grade increase in AST/ALT or total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

The subject's baseline value is defined as the most recent value preceding initiation of the patient's first dose of avelumab.

In the event study treatment is held due to an event the investigator feels is unlikely related or not related to avelumab (e.g. hold study drug per investigator discretion in order to evaluate appropriate attribution to disease versus drug), then resumption of avelumab may proceed according to the medical judgement of the investigator (with maintained accordance to other protocol sections).

If treatment is delayed > 4 weeks (28 days) from the last dose of avelumab, the subject must be permanently discontinued from study therapy, except as may be specified in Sections 9.4, 11.2 and 11.7.

11.3. Guidelines for the Management of Infusion Reaction

Since avelumab is administered via intravenous (IV) infusion, an infusion-related reaction may occur with symptoms possibly including but not limited to fever, chills, rigors, diaphoresis, and headache. In the event of an actual or suspected infusion reaction, avelumab treatment should be modified according to the guidelines listed below in conjunction with any overriding local policies and procedures for the management of infusion-related reactions.

If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgement. The total infusion time for avelumab should not exceed 120 minutes. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue study drug.

Infusion Modifications for Symptoms of Infusion Reaction	
NCI CTCAE Severity Grade	**Avelumab Treatment Modification**
Grade 1 – Mild • Mild transient reaction; • infusion interruption not indicated • intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – Moderate • Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids); • Prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion • Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity Monitor closely for any recurrence or worsening.

Grade 3 or Grade 4 – Severe or Life-threatening Grade 3: • Prolonged (e.g. 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 avelumab infusion immediately • Disconnect bag infusion tubing from the patient. Permanently discontinue avelumab treatment.

IV = intravenous, NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events,
NSAIDs = Non-steroidal anti-inflammatory drugs.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions:

In the event a Grade 2 infusion-related reaction does not improve or worsens after implementation of the modifications indicated in the above table (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the investigator may consider the addition of H2-blocker antihistamines (e.g. famotidine or ranitidine), meperidine, or ibuprofen in supplement to the premedications recommended in Section 9.1. Prophylactic steroids are NOT permitted.

11.4. Management of Severe Hypersensitivity Reaction and Flu-Like Symptoms

As with all monoclonal antibody therapies, avelumab can induce flu-like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis.

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. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable non-steroidal anti-inflammatory drug (NSAID) dose (e.g. ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (e.g. paracetamol or ibuprofen) may be given to patients at the discretion of the investigator.

11.5. Management of Tumor Lysis Syndrome

Because avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of tumor lysis syndrome (TLS). Should this occur, patients should be treated according to local guidelines and the management algorithm (Appendix 6) published by Howard et al.[47]

11.6. Management of Immune-Related Adverse Events (irAEs)

Since inhibition of PD-L1 stimulates the immune system, immune-related adverse events (irAEs) may occur. **Any adverse event judged by the investigator to be possibly, probably or definitely immune-related should be managed according to the guidance in this section for the management of immune-related adverse events, except for circumstances in which local or other standards known to exist are felt by the investigator to present a more medically appropriate course of management.**

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 similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Some potential irAEs described with anti-PD-L1 drugs such as avelumab may be similar to toxicities related to disease (e.g. diarrhea related to adenocarcinoma of the small intestine). In general: Rule out non-inflammatory causes; if non-inflammatory cause is identified, treat accordingly and continue study treatment according to protocol.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. Patients treated for irAEs with IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

MANAGEMENT of GASTROINTESTINAL IMMUNE-RELATED ADVERSE EVENTS (irAEs)		
Diarrhea / Colitis	**Management**	**Follow-Up**
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: Asymptomatic	• Continue avelumab therapy per protocol. • Symptomatic treatment (e.g. loperamide).	• Close monitoring for worsening symptoms. • Educate patient to immediately report worsening. If worsens: • Treat as Grade 2, or Grade 3 to 4.

MANAGEMENT of GASTROINTESTINAL IMMUNE-RELATED ADVERSE EVENTS (irAEs)		
Diarrhea / Colitis	**Management**	**Follow-Up**
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: Abdominal pain; blood in stool	• Delay avelumab therapy per protocol. • Symptomatic treatment.	If improves to Grade ≤1: • Resume avelumab therapy per protocol. If persists > 5-7 days or recurs: • treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): Severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: Life-threatening, perforation	• Withold avelumab for Grade 3 • Permanently discontinue avelumab for Grade 4 or recurrent Grade 3 • 1.0 to 2.0 mg/kg/day methlyprednisolone IV or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider lower endoscopy.	If improves: • Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3) If worsens, 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.

Opiates/narcotics may mask symptoms of perforation. Inliximab should not be used in cases of perforation or sepsis.

MANAGEMENT of DERMATOLOGIC IMMUNE-RELATED ADVERSE EVENTS (irAEs)		
Rash	**Management**	**Follow-Up**
Grade 1 to 2 Covering ≤ 30% body surface area (BSA)	• Continue avelumab therapy per protocol. • Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: • withhold avelumab therapy • Consider skin biopsy. • 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 following steroids taper. If worsens: • Treat as Grade 3 to 4.
Grade 3 Covering > 30% BSA; **Grade 4** life threatening consequences	• Withhold avelumab for Grade 3 • Permanently discontinue for Grade 4 or recurrent Grade 3. • Consider skin biopsy. • Dermatology consult. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤ 1: • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume avelumab therapy following steroids taper (for initial Grade 3).

MANAGEMENT of PULMONARY IMMUNE-RELATED ADVERSE EVENTS (irAEs)		
Pneumonitis	**Management**	**Follow-Up**
Grade 1 Radiographic changes only	• Consider withholding avelumab therapy. • Monitor for symptoms every 2 to 3 days. • Consider Pulmonary and Infectious Disease consults.	• Re-assess at least every 3 weeks. If worsens: • Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	• Withhold avelumab therapy • Pulmonary and Infectious Disease consults. • Monitor symptoms daily, consider hospitalization. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy.	• Re-assess every 1 to 3 days. If improves: • When symptoms return to Grade ≤ 1, taper steroids over at least 1 month and then resume avelumab therapy per protocol following steroids taper and consider prophylactic antibiotics. If not improving after 2 weeks or worsening: • Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	• Permanently discontinue avelumab therapy per protocol. • Hospitalize. • Pulmonary and Infectious Disease consults. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider bronchoscopy, lung biopsy.	If improves to Grade ≤ 1: • Taper steroids over at least1 month. If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil).

Evaluate with imaging and pulmonary consultation as appropriate.

MANAGEMENT of HEPATIC IMMUNE-RELATED ADVERSE EVENTS (irAEs)		
Elevated Liver Function Test (LFT)	**Management**	**Follow-Up**
Grade 1 AST or ALT > ULN to 3.0 x ULN *and/or* total bilirubin > ULN to 1.5 x ULN	• Continue avelumab therapy per protocol.	• Continue liver function monitoring per protocol. If worsens: • Treat as Grade 2 or Grade 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN *and/or* total bilirubin > 1.5 to ≤ 3 x ULN	• Delay avelumab therapy per protocol. • Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: • Resume routine monitoring, resume avelumab therapy per protocol. If elevations persist > 5 to 7 days or worsen: • Treat as Grade 3 or 4.
Grade 3-4 AST or ALT > 5 x ULN *and/or* total bilirubin > 3 x ULN	• Permanently 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/hepatologist • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤ 1: • 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 (BID). • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

MANAGEMENT of RENAL IMMUNE-RELATED ADVERSE EVENTS (Renal irAEs		
Renal Disorder	Management	Follow-Up
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.

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

MANAGEMENT of <u>ENDOCRINE</u> IMMUNE-RELATED ADVERSE EVENTS (irAEs):		
Endocrine Disorder	**Management**	**Follow-Up**

Grade 1 or 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Continue avelumab therapy per protocol.
	• Endocrinology consult if needed
	  • Start thyroid hormone replacement therapy for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate.
	  • Rule out secondary endocrinopathies (i.e. hypopituitarism/hypophysitis
		• Continue hormone replacement/suppression and monitoring of endocrine functions as appropriate.

Grade 3 or Grade 4 Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type I diabetes mellitus)	• Withhold avelumab therapy • Consider hospitalization • Endocrinology consult • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency), or insulin (for Type I diabetes mellitus) as appropriate • Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	• Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	• If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF -1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI • Repeat MRI in one month • Withhold avelumab if mild symptoms of hypophysitis and/or abnormal MRI • Consider hospitalization • Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month • Add prophylactic antibiotics for opportunistic infections	• Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). • In addition for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. • Continue hormone replacement therapy suppression as appropriate.

MANAGEMENT OF CARDIAC IMMUNE-RELEATED ADVERSE EVENTS (irAEs)		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	• Withhold avelumab therapy. • 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.	• 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.
Immune-mediated myocarditis	• Permanently discontinue avelumab. • Guideline based supportive treatment as appropriate as per cardiology consult.* • Methylprednisolone 1 to 2 mg/kg/day	• Once improving, taper steroids over at least 1 month • Prophylactic antibiotics for opportunistic infections. • If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

MANAGEMENT OF OTHER irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Management**	**Management**

Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	• Withhold avelumab therapy pending clinical investigation	• If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy • If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of **Grade 3** irAE	• Withhold avelumab therapy • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Specialty consult as appropriate	• If improves to Grade ≤ 1: • Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	• Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/dayprednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Specialty consult as appropriate	• If improves to Grade ≤ 1: • Taper steroids over at least 1 month.
Grade 4	• Permanently discontinue avelumab therapy • 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed • Add prophylactic antibiotics for opportunistic infections • Specialty consult.	• If improves to Grade ≤ 1: • Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	• Permanently discontinue avelumab therapy • Specialty consult	

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

12. DRUG FORMULATION, SUPPLY AND STORAGE

12.1. Description of Avelumab

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143,832 Daltons) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1.

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (i.v.) administration.

12.2. Packaging and Labeling of Avelumab

Avelumab will be provided by EMD Serono. Avelumab drug product is a sterile solution intended for intravenous (i.v.) administration.
Avelumab drug product is a sterile, clear, and colorless concentrate for solution typically presented at concentrations of 10 mg/mL and 20 mg/mL in single use glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.
Each single-use 10 mg/mL vial typically contains 80 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.5) containing Mannitol, Methionine, and Polysorbate 20 (Tween 20).
Each single-use 20 mg/mL vial typically contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol and Polysorbate 20 (Tween 20).
For avelumab drug product, only excipients that conform to the current European Pharmacopeia (Ph. Eur.) and/or the current United States Pharmacopeia (USP) are used.

12.3. Storage of Avelumab

Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen.

Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Rough shaking of the solution must be avoided.

For application in clinical trials, avelumab drug product must be diluted with 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag.

It is recommended that diluted avelumab solution be used immediately. The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately 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.

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

12.4. Accountability of Avelumab

Discarded volumes of avelumab should be disposed of as clinical waste. Partially full and empty vials may be destroyed at the site by the appropriate site personnel (e.g. Pharmacist or Study Nurse/Coordinator) following local environmental requirements and institutional policies. All

destruction must be fully documented on an Investigational Product Accountability Log (IPAL) or similar at the time of destruction.

13. MEASUREMENT of EFFECT

13.1. Definitions

For purposes of this study, patients should be re-evaluated for response every 8 weeks. Response and progression will be evaluated using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1) and immune-related response criteria (irRC). Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. If a patient is found to have disease progression by RECIST, at the discretion of the treating physician, the patient may remain on study. Baseline evaluation of disease status by CT or MRI required within 28 days prior to first dose of avelumab. The first scheduled re-scan should be performed and evaluated 7 to 8 weeks after Cycle 1, Day 1 treatment, with subsequent scheduled scans intended every 8 to 9 weeks thereafter. If progression is confirmed by irRC, the patient should typically be removed from study (i.e. in the absence of therapeutic benefit and an alternative agreement and arrangement specified by protocol). If irRC show the patient to not have disease progression, the patient may remain on study.

Evaluable for toxicity: All patients will be evaluable for toxicity from time of their first treatment with avelumab.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

If a patient discontinues study treatment for reasons clearly not related to study treatment, after completing fewer than one planned infusion of avelumab, and/or receiving <75% of the total intended dose of avelumab over the first cycle of treatment + an additional 14 days (i.e. first 28 days after initiating patient's first dose of avelumab), then that patient will be considered not evaluable for response to study treatment and may be replaced with a new patient.

13.2. Disease Parameters

13.2.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

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

13.2.2 Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

13.2.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

13.2.4 Specifications by methods of measurements

Measurement of lesions:

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks (28 days) before the beginning of study treatment.

Method of assessment:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Guidelines have defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for bodyscans).

  Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the

measurable tumor has met criteria for response or stable disease, in order to differentiate between response (or stable disease) and progressive disease.

13.3. Response Criteria

13.3.1 **Target lesions**

When more than one measurable lesion is present at baseline: All lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions, with repeatable measurements recorded and measured at baseline. (In instances where patients have only one or two organ sites involved, a maximum of two and four lesions will respectively be recorded.)

13.3.2 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

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

13.3.3 Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

13.3.4 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of applicable tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)

13.3.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease; and will also take into consideration the appearance of new lesions, as well as post-treatment assessments and any new therapy introduced before progression. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

Time point response:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non PD or not all evaluated	No	PR
SD	Non PD or not all evaluated	No	SD
Not all evaluated	Non PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR= complete response, PR= partial response, PD= progressive disease, SD= stable disease, NE= not evaluable.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.*

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

13.4. Duration of Response

13.4.1 **Duration of overall response**

The duration of response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

13.4.1 **Duration of stable disease**

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13.5. Immune-Related Response Criteria

13.5.1 **Increasing clinical experience indicates that traditional response criteria** (e.g. Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to fully characterize activity in the new era of targeted therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease have been shown to occur after an initial increase in tumor burden characterized as progressive disease according to traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. Immune-related response criteria (irRC) attempt to enhance characterization of new response patterns that have been observed with immunotherapeutic agents (e.g. ipilimumab and nivolumab).

13.5.2 **Glossary of Immune-Related Response Terminology**

Term	Definition
SPD	Sum of the Products of the two largest perpendicular Diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related Complete Response
irPD	immune-related Progressive Disease
irPR	immune-related Partial Response
irSD	immune-related Stable Disease
irBOR	immune-related Best Overall Response

13.5.3 **Baseline Assessment Using Immune-Related Response Criteria (irRC)**

- Step 1: Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

- Step 2: Calculate the Sum of the Products of the two largest perpendicular Diameters (SPD) of all of these index lesions:

$$\text{SPD} = \sum_{i} (\text{Largest diameter of lesion i}) \text{ x } (\text{Second largest diameter of lesion i})$$

13.5.4 **Post-baseline Assessments Using irRC**

- Step 1: Calculate the SPD of the index lesions.

- Step 2: Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

- Step 3: Calculate the SPD of the new, measurable lesions.

- Step 4: Calculate the tumor burden:

  Tumor burden = SPDindex lesions + SPDnew, measurable lesions

- Step 5: Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

- Step 6: Derive the overall response using the table below:

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented.
irPR	Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation.
irPD	Increase in tumor burden ≥ 25% relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

13.5.5 **Determination of Immune-Related Best Overall Response (irBOR)**

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

13.6. Response Review and Central Tumor Assessments

All responses, if any, may be reviewed by an expert(s) independent of the study at the study's completion. In addition, at the end of treatment, all scans (baseline and through disease progression) may be requested via a CD and sent to the Vanderbilt Cancer Imaging Support Laboratory for central review and assessment.

14. SAFETY REPORTING of ADVERSE EVENTS

14.1. General

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered possibly, probably or definitely related to avelumab, all events of death, and any study-specific issue of concern.

Adverse event collection and reporting is a routine part of every clinical trial. Each adverse event will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, dated June 14, 2010, currently locatable via the following URL: < http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf >.

For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild**: An event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate**: An event not resulting in disability or incapacity but which requires intervention;
- **Severe**: An event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening:** An event in which the patient was at risk of death at the time of the event;
- **Fatal:** An event that results in the death of the patient.

Information on all adverse events, whether serious or not, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Reporting period: Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.
Laboratory and vital sign abnormalities are to be recorded as Adverse Events only if they are medically relevant as judged by the investigator (e.g. symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion). Unless otherwise specified by protocol or a patient's study physician, abnormal laboratory values of Grade 1 and Grade 2 will be deemed Not Clinically Significant (NCS) and are not required to be individually noted or recorded within the study data.

Baseline disease-related signs and symptoms which are initially recorded as medical history, will subsequently be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other

applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

14.2. Risks Associated with Avelumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related adverse events, specifically the induction or enhancement of autoimmune conditions. AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, myositis, and myasthenia gravis, have been observed in studies involving immunomodulators.

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.

A more detailed safety profile of avelumab is provided in the avelumab Investigator's Brochure.

14.3. Safety Parameters and Definitions

14.3.1 **Adverse Event (AE)**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. Progressive disease will not be considered an adverse event.
An adverse event includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as biopsy).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

14.3.2 **Serious adverse event (SAE)**

An AE should be classified as an SAE if the following criteria are met:

- It results in death.
- It is life threatening (i.e. the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization.

- It results in persistent or significant disability/incapacity (i.e. the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

14.4. Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e. start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines:

Yes
There is a plausible temporal relationship between the onset of the AE and administration of avelumab, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to avelumab; and/or the AE abates or resolves upon discontinuation of avelumab or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than avelumab (e.g. pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to avelumab administration (e.g. cancer diagnosed 2 days after first dose of study drug).

14.4.1 Expectedness
Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

- Unexpected: An adverse event is considered <u>unexpected</u> when it varies in nature, intensity or frequency from information provided in the current adverse event list, the

Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

14.4.2 **Attribution**

The investigator must attempt to determine if there exists reasonable possibility that an adverse event or serious adverse event is related to the use of the study treatment. Attribution of adverse events should be described as unrelated; or unlikely, possibly, probably, or definitely related to the study treatment:

Attribution	Description
Unrelated	AE ***is clearly NOT related*** to the intervention.
Unlikely	AE ***is doubtfully related*** to the intervention.
Possible	AE ***may be related*** to the intervention.
Probable	AE ***is likely related*** to the intervention.
Definite	AE ***is clearly related*** to the intervention.

For additional purpose of any applicable binary regulatory reporting, an event should be considered *Unrelated* to study treatment when its attribution is felt by the investigator to be either Unrelated or Unlikely related to study treatment. Similarly, an event should be considered *Related* to study treatment, when its attribution is felt to be either Possibly, Probably, or Definitely related to study treatment.

14.5. Reporting Procedures

14.5.1 **Specific Instructions for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

14.5.2 **Diagnosis versus Signs and Symptoms**

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

14.5.3 **Deaths**

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study CRF and not reported as an SAE.

14.5.4 **Pre-existing Medical Conditions**

A pre-existing medical condition is one that is present prior to initiation of protocol specified treatment. Such conditions should be reported as medical and surgical history. A pre-existing

medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

14.5.5 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

14.5.6 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant while enrolled in the study. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via fax or email. A pregnancy report will be generated and sent to EMD Serono Drug Safety. Pregnancy should not be recorded on the Adverse Event CRF. Unless otherwise agreed to and approved by the Investigator, EMD Serono and the IRB, the patient should discontinue study drug. The investigator or medical designee should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g. an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF.

A Clinical Trial Pregnancy Reporting Form and cover sheet should be completed and faxed or emailed to EMD Serono Drug Safety or its designee immediately (i.e. no more than 24 hours after learning of the pregnancy), using contact information provided to investigators.

14.5.7 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the informed consent form to immediately inform the investigator if their partner becomes pregnant at any point while they are enrolled on the study. Male patients who received study treatment should not attempt to father a child until end of study. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and faxed or emailed to EMD Serono Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will be asked to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator or designee will update the Pregnancy Report CRF with additional

information on the course and outcome of the pregnancy. An investigator or medical designee who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

14.5.8 **Abortions**

Any spontaneous abortion should be classified as an SAE (as the Sponsors consider spontaneous abortions to be medically significant events), recorded on the Adverse Event CRF, and reported to EMD Serono Drug Safety immediately (i.e. no more than 24 hours after learning of the event).

14.5.9 **Congenital Anomalies/Birth Defects**

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF, and reported to EMD Serono Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

14.5.10 **Post-Study Adverse Events**

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior avelumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

14.5.11 **Safety Reconciliation**

The Sponsor-investigator agrees to conduct reconciliation for the product. EMD Serono and the Sponsor-investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor-investigator and EMD Serono will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

14.5.12 **Adverse Events of Special Interest (AESIs)**

Any adverse event that is suspected to be a potential immune-related adverse event (irAE) is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 11.7. AESIs are reported according to the general AE reporting rules specified in Section 14.5.

14.5.13 **Serious Adverse Events**

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the OnCore SAE form and the Vanderbilt SAE form located in OnCore documents.

The form must be fully completed and emailed (preferred), faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: Coordinating.Center@Vanderbilt.edu
FAX: (615) 875-0040

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

14.5.14 **Institutional Review Board**

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

14.5.15 **Food and Drug Administration (FDA)**

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to avelumab (as determined by the sponsor-investigator) will be reported to the Food and Drug Administration via MedWatch 3500A (available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf).

Submissions by the sponsor can be submitted via fax or email and must be addressed to the Regulatory Project Manager in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA.

14.5.16 **EMD Serono**

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Sponsor/Principal Investigator* will assume all responsibility for submitting the reportable event(s) to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.:
Serious Adverse Events
Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
Occupational exposure (even if not associated with an adverse event)
Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

The completed MedWatch/case report should be faxed or emailed immediately upon completion to EMD Serono Drug Safety at:

Fax: +49 6151 72 6914
or
E-mail: ICSR_CT_GPS@merckgroup.com

Specifying:

- Protocol Number and/or Title
- Subject Number
- Site Number/PI Name
- SAE/Onset Date

Relevant follow-up information should be submitted to EMD Serono Drug Safety as soon as it becomes available.

Adverse Events of Special Interest (AESIs) will be transmitted to EMD Serono within 15 calendar days of the Awareness Date. All non-serious avelumab AEs originating from the study will be forwarded to EMD Serono monthly.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up;
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form;
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally EMD Serono may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the EMD Serono Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to EMD Serono Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is currently available at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm2007307.htm

14.5.17 **Additional Reporting Requirements for IND**

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report
The investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of avelumab. An unexpected AE is one that is not already described in the avelumab Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA and EMD Serono within 7 calendar days of first learning of the event.

15 Calendar Day Written Report
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of avelumab. An unexpected AE is one that is not already described in the avelumab Investigator's Brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA, EMD Serono, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g. summary letter).

Contact Information for IND Safety Reports
FDA fax number for IND safety reports:
Fax: (800) FDA-0178.

All written IND safety reports submitted to the FDA by the investigator must also be submitted via fax or email to the following:
EMD Serono Drug Safety Fax: +49 6151 72 6914or **Email:** ICSR_CT_GPS@merckgroup.com

For questions related to safety reporting, please contact EMD Serono Drug Safety:
Fax: +49 6151 72 6914

Or Email: GlobalDrugSafety@merckgroup..com

14.5.18 IND Annual Reports
Copies of all IND annual reports submitted to the FDA by the Sponsor-investigator should be sent to the EMD Serono Drug Safety designee via fax or email.

14.5.19 Study Close-Out
Any study report submitted to the FDA by the Sponsor-investigator should be copied to EMD Serono. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to EMD Serono. Copies of such reports should be faxed, emailed, or mailed to the assigned Clinical Operations contact for the study.

15. DATA SAFETY AND MONITORING

15.1. Data Management and Reporting

Data will be collected using a centralized electronic case report form called ON-line Clinical Oncology Research Environment (Oncore), located at
< http://www.vicc.org/ct/research/oncore.php > .

Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. The system is capable of storing basic protocol information (e.g. IRB approval dates, dates for annual renewals) and clinical trials research data, and it fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring.

Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all VICCC clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource.

Specified site members will submit all pertinent regulatory documents to the Coordinating Center Data Manager, who will store it in a secure location.

The Principal Investigator or designee will inform EMD Serono as defined in any established Safety and Data Exchange Agreement (SDEA) of any serious adverse event, and will inform the Vanderbilt IRB in accordance with IRB policy. The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the treating investigator or site staff will be responsible for detecting, documenting, and report AEs and SAEs, as detailed in the protocol. If any problem is identified related to the conduct of this research, the VICC Data Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

15.2. Meetings

This trial will be monitored by the VICC Gastrointestinal Research Team. The GI research team is composed of Medical Oncologists, Research Nurses, Data Managers, and Regulatory Specialists. The GI Research Team meets on a monthly basis to discuss all AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, reviews, etc. pertaining to all GI team cancer studies. This particular study will be thoroughly reviewed during these meetings. These monthly meetings have minutes recorded which are reviewed on a monthly basis by the Physician Leader of the Gastrointestinal Research Team.

15.3. Monitoring

This trial will be monitored continuously by the study's Protocol Chair and by the Gastrointestinal Research Team at VUMC. Additionally, the Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.
The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored, investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The investigator will allow the VICC-DSMC designee access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the data case report forms (CRFs) and for the review of the data collection process. The VICC-DSMC designee will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

The investigator and the investigational site staff must be available to meet with the VICC-DSMC designee in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the research compliance coordinator.

Additionally, the Coordinating Center has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards to ethics, protocol adherence, integrity, validity of the data recorded on the CRFs, and adherence to regulations regarding Good Clinical Practice (GCP) and the protection of human subjects.

In accordance with applicable regulations, GCP, and Coordinating Center procedures, sites will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Coordinating Center

requirements.

During the course of the study, the Coordinating Center will routinely monitor sites for protocol compliance, compare CRFs with individual subjects' original source documents, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subjects' medical records will be performed in a manner to ensure that subjects' confidentiality is maintained. Monitoring visits will primarily be conducted remotely, and sites are required to provide the appropriate source documentation in order to allow for proper oversight per GCP. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved. In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

In accordance with HIPAA and associated privacy regulations, a subject's authorization to use personally identifiable health information may be required from each subject before commencement of research activities. This authorization document must clearly specify what parties will have access to a subject's personal health information, for what purpose and for what duration.

VICC Multi-Institutional Coordinating Center

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

15.4. Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant.

The investigator or designee may maintain records separate from the case report forms in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when a designee of the Data Safety Monitoring Committee (DSMC) of the Vanderbilt-Ingram Cancer Center (VICC) audits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All

information obtained from source documents will be kept in strict confidentiality. Source data sent as supporting documentation to regulatory authorities for serious adverse events will be de-identified to preserve confidentiality.

To enable evaluations and/or audits from Health Authorities and Vanderbilt the investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed online. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will be generated and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

16. REGULATORY CONSIDERATIONS

16.1. Pre-Study Documentation

Prior to initiating the trial, the investigator will secure the following documents:

- A signed FDA Form 1572
- A current *curriculum vitae* for the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A copy of the current medical license for the investigator and each sub-investigator listed on the FDA Form 1572
- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- A copy of the IRB-approved informed consent document
- The current IRB membership list for the reviewing IRB
- A completed financial disclosure form for the investigator and all sub- investigators
- Current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory.

16.2. Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by both EMD Serono and the IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the Sponsor.

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB and the FDA.
The Protocol Chair (or designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the institutional participants.

16.3. Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

16.4. Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described within:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described within the above and thereby to adhere to the principles of Good Clinical Practice with which the above conform.

16.5. Confidentiality

It is the responsibility of the investigator to insure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

16.6. Records Retention

The investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB correspondence, etc) for at least 2 years after all investigations have been discontinued. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records that must be retained include case report forms, signed informed consents, correspondence with the IRB, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/enrollment logs.

16.7. Study Termination

The investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Decision by EMD Serono to modify or discontinue the development or manufacture of avelumab
- A request to discontinue the study by the IRB or FDA.

The investigator will promptly notify EMD Serono, the IRB and FDA if the study is terminated for any reason.

17. STATISTICAL CONSIDERATIONS

17.1. Study Design / Endpoints

The primary objective of this clinical trial is to estimate the objective response rate (ORR) from the best response a patient experiences prior to progression (using RECIST v1.1 and irRC). Twenty-five patients will be enrolled on this clinical trial. This regimen will be considered sufficiently active to

warrant further study in more definitive trials if 4 patients experience an objective response among 25 treated.

17.2. Sample Size / Accrual Rate

This investigator-initiated study intends single-site enrollment limited to patients at Vanderbilt University Medical Center.

About 25 patients evaluable for disease response are anticipated to enroll in approximately 24-36 months.

17.3. Statistical Analysis Plan

Demographic, baseline patient characteristics, and study outcomes are intended to be summarized graphically and numerically. Adverse events will be classified by type, incidence, severity and causality according to CTCAE v4.03. All adverse events will be summarized by patient, and all patients who received at least one cycle of the therapy (or discontinued due to treatment-related adverse event) will be included in the safety profile.

Continuous (e.g. age at on-study date) variables will be summarized using the 25th, 50th (median), and 75th percentiles, the range, as well as the mean and standard deviation. Categorical variables, (e.g. adverse events) will be reported as frequencies. 95% confidence intervals will be reported for all outcomes. The distribution of PFS and OS will be estimated using the Kaplan-Meier (product-limit) estimate with standard errors based on Greenwood's formula. No comparative statistical tests are planned for this study.

The Wilson 95% confidence intervals for 0 to 13 objective responses among 25 patients treated are listed in **Table 3**:

Table 3. Ninety-five percent (Wilson) confidence intervals for objective response rate among 25 patients.

Number of Objective Responses	Objective Response Rate (%)	Lower Limit (%)	Upper Limit (%)
0	0	0	13.3
1	4	0.2	19.5
2	8	2.2	25.0
3	12	4.2	30.0
4	16	6.4	34.6
5	20	8.9	39.1
6	24	11.5	43.4
7	28	14.3	47.6
8	32	17.2	51.6
9	36	20.2	55.5
10	40	23.4	59.3
11	44	26.7	62.9
12	48	30.3	66.5
13	52	33.5	70.0

Considering the published data[47,48] regarding the responses to standard of care chemotherapy regimens, we propose that observing the same or better clinical outcomes with avelumab monotherapy would warrant further therapeutic study in patients with advanced small intestinal adenocarcinoma.

Twenty-five patients will be enrolled on this clinical trial. We assume a one-sided type I error rate of 5% using a one-sample binomial test and desire 80% power to reject the null hypothesis that this regimen is ineffective if it elicits an objective response rate of 5%. Twenty-five patients provide 80% power to reject the null hypothesis if the true objective response rate (ORR) of this regimen is 21% or greater. This regimen will be considered sufficiently active to warrant further study in more definitive trials if 4 or more patients among 25 treated experience an objective response.

17.4. Reporting and Exclusions

All patients included in the study must be assessed for safety, tolerability, and response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following response categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All patients meeting the eligibility criteria and received study drug for 2 weeks should be included in the main analysis of the clinical benefit rate. Patients in above response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration should not result in exclusion from the analysis of the response and clinical benefit rate.

18. REFERENCES

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APPENDIX 1

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines[49]

CATEGORIZING LESIONS AT BASELINE

Measurable lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

Non-measurable disease

- Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.
- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Target Lesions

- All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

Non-target disease

- All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Lesions

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for

target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate: Progression has not been documented, AND
  - One or more target measurable lesions have not been assessed; OR
  - Assessment methods used were inconsistent with those used at baseline; OR
  - One or more target lesions cannot be measured accurately (e.g. poorly visible unless due to being too small to measure); OR
  - One or more target lesions were excised or irradiated and have not reappeared or increased.

<u>Non-target disease</u>

- CR: Disappearance of all non-target lesions and normalization of applicable tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or applicable tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

<u>New Lesions</u>

- The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective/Subjective Progression

- Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Objective Response Status at each Evaluation:

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used.

Objective Response Status at each Evaluation for Patients with Non-Target Disease Only:

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

DETEMINATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

APPENDIX 2

Immune-Related Response Criteria Derived From RECIST 1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1/anti-PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[50,51]

Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[52,53]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria. [52,53]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST).[54]

For irRECIST, only target and measurable lesions are taken into account. In contrast to RECIST v1.1, irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and
- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

Immune-Related Response Evaluation Criteria in Solid Tumours (irRECIST) is defined as follows:

- Overall immune-related complete response (irCR):
  Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to < 10 mm.
- Overall immune-related partial response (irPR):
  Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥ 30%.
- Overall immune-related stable disease (irSD):

Sum of the diameters (longest for nonnodal lesions, shortest for nodal lesions) of target and new measurable lesions is neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).

- Overall immune-related progressive disease (irPD):
  Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (i.e. added to the target lesion measurements). A lymph node has to be ≥ 15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.
New non-measurable lesions: Do not define progression but preclude irCR.

Overall responses derived from changes in index, non-index, and new lesions are outlined in the below table:

Overall Response Derived from Changes in Index, Non-index and New Lesions:

Measurable response	Non-measurable response		Overall response using irRECIST[b]
Index and New Measurable Lesions (Tumor Burden)[a]	Non-Index Lesions	Measurable Lesions	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

a. Decrease assessed relative to baseline.
b. Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix 3

Cockcroft-Gault (CG) equation for the estimation of creatinine clearance

$$eCrCl\ (mL/min) = \frac{(140 - age\ in\ years)\ x\ (weight\ in\ kg)\ x\ (0.85\ if\ female)}{72\ x\ (serum\ creatinine\ in\ mg/dL)}$$

Appendix 4
Acceptable Contraception

Female patients of childbearing potential and male patients able to father children who have female partners of childbearing potential must agree to use at least one highly effective method of contraception, defined as methods with a failure rate of less than 1% per year when used consistently and correctly, as well as one additional effective method. Appropriate contraceptive methods are required at least 15 days prior to starting therapy, throughout the study, and for at least 30 days after the study participant's final dose of avelumab.
Females of childbearing potential are defined as those who are not surgically sterile or post-menopausal (i.e. patient has not had a bilateral tubal ligation, a bilateral oophorectomy, or a complete hysterectomy; or has not been amenorrheic for 12 consecutive months without an alternative pathological or physiological cause). Postmenopausal status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women.

Male patients able to father children are defined as those who are not surgically sterile (i.e. patient has not had a vasectomy).
A study physician or clinical designee shall counsel female patients of childbearing potential and male patients able to father children who have female partners of childbearing potential, regarding the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the use of acceptable contraceptives.
Subjects must agree to use at least one method of highly effective contraception and one additional effective method. The acceptable methods are listed below:
Highly effective contraceptive methods (must use at least one):

1. Combined (estrogen and progesterone containing) hormonal contraceptive associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
2. Progesterone-only hormonal contraceptive associated with inhibition of ovulation[1] (oral, injectable, implantable[2])
3. Intrauterine device (IUD)[2]
4. Intrauterine hormone-releasing system (IUS)[2]
5. Bilateral tubal occlusion[2]
6. Vasectomized partner[2,3]
7. Abstinence defined as complete avoidance of heterosexual intercourse

   Complete abstinence is defined as complete avoidance of heterosexual intercourse, when consistent with the patient's preferred and established lifestyle, is an acceptable form of contraceptive for purposes of the study. Periodic abstinence (e.g. calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable forms of contraceptive in this study. In the event the subject chooses to forego complete abstinence, acceptable methods of contraceptive (see above lists) must be discussed with the study physician or clinical designee.

Notes:
[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method
[2]Contraception methods in the context of this guidance are considered to have low user dependency

[3]Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success

Additional effective contraceptive methods (must use at least one if only using one highly effective method listed above):

1. Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository)
2. Diaphragm
3. Cervical cap

APPENDIX 5

New York Heart Association Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Abbreviations: NYHA = New York Heart Association