DF/HCC Protocol #: 16-322

TITLE: A Phase 2, Two-Group, Two-Stage, Open-Label Study of Avelumab in Patients with MSS, MSI-H and POLE-mutated Recurrent or Persistent Endometrial Cancer, Avelumab / Talazoparib in Patients with MSS Recurrent or Persistent Endometrial Cancer, and Avelumab / Axitinib in Patients with MSS Recurrent or Persistent Endometrial Cancer

Coordinating Center: Dana-Farber/Harvard Cancer Center

Principal Investigator (PI): Panagiotis A. Konstantinopoulos MD, PhD
Dana-Farber Cancer Institute
YC-1424, 450 Brookline Ave
Boston, MA 02215
Telephone: 617-632-5269
Fax: 617-582-7921
Panagiotis_Konstantinopoulos@dfci.harvard.edu

Other Investigators: Mary Buss, MD
Beth Israel Deaconess Medical Center
mbuss@bidmc.harvard.edu

Richard Penson, MD
Massachusetts General Hospital
Penson.Richard@mgh.harvard.edu

Statistician:
Su-Chun Cheng, ScD
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Phone: 617-582-7257
SCheng@jimmy.harvard.edu

Responsible Project Manager:
Madeline Polak
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Phone: 617-632-3743
Madeline_Polak@dfci.harvard.edu

Responsible Research Nurse:
Christin Whalen, RN
450 Brookline Avenue
Boston, MA 02215
Phone: 617-582-7738
Fax: 617-582-7921
Christin_Whalen@dfci.harvard.edu

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SCHEMA

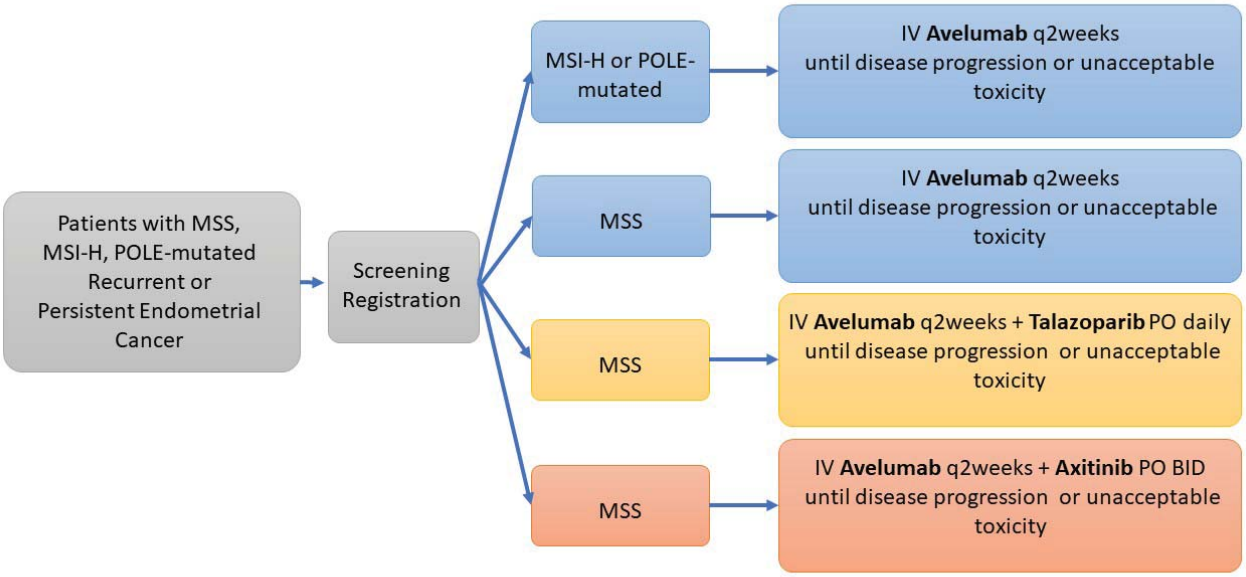
This is a non-randomized, open-label, two-cohort, two-stage, phase 2 trial, of avelumab in two cohorts of endometrial cancer patients: i) MSI or POLE-mutated endometrial cancers (MSI/POLE cohort) and ii) MSS endometrial cancers (MSS cohort).

Given that avelumab single agent activity in the MSS cohort did not meet study criteria to move on to stage II, we are now adding a new cohort of MSS patients who will be receiving avelumab plus talazoparib to assess whether this combination will be efficacious against these tumors.

MSI/POLE Cohort: Avelumab as a 1-hour intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicity (one cycle=28 days including two infusions)

MSS Cohort: Avelumab as a 1-hour intravenous (IV) infusion once every 2 weeks and oral talazoparib every day until disease progression or unacceptable toxicity (one cycle=28 days including two infusions)

MSS Cohort, additional: Avelumab as a 1-hour intravenous (IV) infusion once every 2 weeks and oral axitinib twice daily, until disease progression or unacceptable toxicity (one cycle = 28 days, including two infusions)


Patients with MSS, MSI-H, POLE-mutated Recurrent or Persistent Endometrial Cancer
Screening Registration
MSI-H or POLE-mutated
IV **Avelumab** q2weeks until disease progression or unacceptable toxicity
MSS
IV **Avelumab** q2weeks until disease progression or unacceptable toxicity
MSS
IV **Avelumab** q2weeks + **Talazoparib** PO daily until disease progression or unacceptable toxicity
MSS
IV **Avelumab** q2weeks + **Axitinib** PO BID until disease progression or unacceptable toxicity

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1. SYNOPSIS & OBJECTIVES

1.1 Study Design

This is a non-randomized, open-label, multi-cohort, two-stage, phase 2 trial, of:

1. avelumab in MSI or POLE-mutated endometrial cancers (MSI/POLE cohort)
2. avelumab in MSS endometrial cancers (MSS cohort)
3. combination of avelumab + talazoparib in MSS endometrial cancers (MSS cohort)
4. combination of avelumab + axitinib in MSS endometrial cancers (MSS cohort)

It entails a two-stage Optimum design for each MSI/POLE and MSS cohort to inform whether that cohort's treatment (avelumab alone, avelumab + talazoparib, or avelumab + axitinib) has significant clinical activity that is worthy of further evaluation in each of the cohorts.

Statistical considerations are developed for co-primary objectives to evaluate the objective response rate (ORR) and rate of progression-free survival at 6 months (PFS), with a two-stage design that allows for early stopping for futility for each cohort.

Maximum target enrollment is 105, 35 per cohort, assuming that each cohort will meet criteria for moving into stage II. The total sample size will be adjusted to allow for replacement of participants who never began protocol therapy for reasons including ineligibility, inevaluability, and participant drop out. While the maximum target accrual is 105 patients, up to 115 patients can be enrolled to allow for replacement.

1.2 Primary Endpoints

Primary endpoints for avelumab & avelumab/talazoparib:
To assess the activity of avelumab in patients with recurrent or persistent endometrial cancer classified by MSI/POLE and MSS genomic cohorts as well as the activity of avelumab plus talazoparib in patients with recurrent MSS endometrial cancers as determined by the frequency of patients who survive progression-free for at least 6 months (PFS6) after initiating therapy or have objective tumor response.

Co-primary endpoints for combination avelumab/axitinib:

a. To assess the clinical activity of combination avelumab/axitinib in patients with MSS recurrent or persistent endometrial cancer, as determined by the frequency of patients who survive progression-free for at least 6 months (PFS6)
b. To assess the clinical activity of combination avelumab/axitinib in patients with MSS recurrent or persistent endometrial cancer, as determined by the objective response rate (ORR) measured by RECIST 1.1

1.3 Secondary Endpoints

Secondary endpoints for avelumab & avelumab/talazoparib:

a. To determine the duration of progression-free survival and overall survival for each cohort.

b. To determine the nature and degree of toxicity of avelumab or avelumab/talazoparib for each cohort as classified by the common terminology criteria for adverse events (CTCAE) version 4.0.
c. To determine Immune-related objective response rate for each cohort as described in Section 11.2
d. Immune-related progression-free survival (irPFS) rate for each cohort defined as time from cohort assignment to death or to immune-related progression of disease (irPD) as defined in Section 11.2.

Secondary endpoints for combination avelumab/axitinib:

a. To assess the clinical activity of combination avelumab/axitinib as measured by median progression-free survival (PFS) and median overall survival (OS)
b. To assess the clinical activity of combination avelumab/axitinib as measured by the immune-related ORR, as measured by irRECIST criteria
c. To assess the clinical activity of combination avelumab/axitinib as measured by the immune-related PFS (irPFS)
d. To determine the safety and toxicity of combination avelumab/axitinib, as classified by the CTCAE v4.1

1.4 Exploratory Endpoints

- Assessment of CD3+ tumor infiltrating lymphocytes (TILs) and circulating lymphocytes, CD8+ TILs, CD8+/CD4+FOXP3+ TIL ratio, CD137+CD8+ TILs, D137+CD8+/CD4+FOXP3+ TIL ratio and correlation with response
- Assessment of myeloid, stromal and other immunoactive cell types from blood, tissue and fluid samples and correlation with response
- Assessment of the expression pre-, during, and at time of progression of immune checkpoints including TIM-3, LAG-3, CTLA-4, PD-L2, PD-L1, PD-1, IDO and correlation with response
- Whole exome sequencing (WES) for specific DNA gene repair mutations and neoantigen assessment as well as for single nucleotide polymorphisms (SNPs) in immunologically relevant genes and correlation with response
- Presence of anti-avelumab antibodies and correlation with response

2. BACKGROUND

2.1 Study Disease

2.1.1 Epidemiology

Endometrial cancer is the most common gynecologic malignancy with an annual incidence of 40,000 cases (Jemal *et al.*, 2009). The majority of women with endometrial cancer are diagnosed with early stage cancer which is typically treated surgically with overall excellent outcomes. However, women with recurrent disease or metastatic disease have limited treatment options. These patients account for the approximate 8,000 annual death rate from this cancer (Jemal *et al.*, 2009). As such, this disease represents an important unmet medical need. The recent identification of distinct genomic subtypes of endometrial cancer from The Cancer Genome Atlas has opened the

opportunity to stratify response to therapy by subtype generally and specifically has identified distinct subtypes with high mutational burdens and a correspondingly increased number of neoepitopes that may be particularly likely to respond to checkpoint blockade and other immune-activating therapies (The Cancer Genome Atlas Research Network, 2013).

2.1.2 Current Treatment Paradigms

There have been several randomized studies performed to ascertain the optimal therapy patients with recurrent or metastatic disease. These studies have focused on three active chemotherapy agents identified to have significant activity as monotherapy in phase II trials: doxorubicin, platinum agents, and paclitaxel. In GOG-0107 (Thigpen *et al.*, 2004), 281 women were randomized to doxorubicin alone (60 mg/m2) versus doxorubicin (60 mg/m2) plus cisplatin (50 mg/m2) (AP). There was a statistically significant advantage to combination therapy with regard to response rate (RR) (25% versus 42%; p=0.004) and PFS (3.8 vs 5.7 months; HR 0.74 [95% CI 0.58, 0.94; p=0.14), although no difference in OS was observed (9 vs 9.2 months). Phase II data published by the GOG in 1996 (Ball *et al.*, 1996) demonstrated that paclitaxel had significant single agent activity with a response rate of 36% in advanced or recurrent endometrial cancer. Thus 317 patients were randomized to paclitaxel and doxorubicin or the standard arm of AP in GOG-0163 (Fleming et al., 2004b). This trial failed to demonstrate a significant difference in RR, PFS, or OS between the two arms, and AP remained the standard of care. However, since both platinum and paclitaxel had demonstrated high single agent activity, there was a strong interest in including paclitaxel and cisplatin in a front-line regimen for advanced and recurrent endometrial cancer. Subsequently, GOG-0177 (Fleming et al., 2004a) randomized 263 patients to AP versus TAP: doxorubicin (45 mg/m2) and cisplatin (50 mg/m2) on day 1, followed by paclitaxel (160 mg/m2 IV over 3 hours) on day 2 (with G-CSF support). TAP was superior to AP in terms of ORR (57% vs 34%; p<0.01), median PFS (8.3 vs 5.3 months; p<0.01) and OS with a median of 15.3 (TAP) versus 12.3 months (AP) (p=0.037). This improved efficacy came at the cost of increased toxicity. In GOG-0209 TAP was compared in a randomized fashion to paclitaxel and carboplatin (CT) in an attempt to address the issue of toxicity; CT was found to be not inferior to TAP in terms of PFS and OS. At the reported interim analysis, the median PFS was 14 months in both arms (HR, 1.03), while median OS was 32 months vs. 38 months in patients treated with CT vs. TAP (not significant, HR, 1.01). Additionally, CT was better tolerated than TAP.

Given these studies, first line treatment for metastatic or recurrent disease remains a combination regimen of a platinum agent with either a taxane, anthracycline or both. However, once this initial therapy has been delivered, either in the adjuvant or advanced disease setting, there are limited treatment options, with no established standard options available.

Hormonal therapies, when given to chemotherapy naïve patients, can result in response rates of up to 33%, but responses are of short duration (median PFS of approximately 3 months) (Lentz *et al.*, 1996; Thigpen *et al.*, 1999; Thigpen *et al.*, 2001; Whitney *et al.*, 2004).

Phase II studies of the rapalogs (everolimus, temsirolimus, AP23573), which target mTOR (specifically mTORC1), a downstream target of AKT, suggest the clinical utility of these agents (Colombo et al., 2013; Oza et al., 2008; Slomovitz et al., 2010). Trials of single agent use of these drugs in pre-treated endometrial cancer revealed modest results, with both objective responses as well as clinically significant disease stabilization. Briefly, the investigators of everolimus reported a

0% partial response and 44% of patients with stable disease at 8 weeks. The study of temsirolimus revealed a 7.4% partial response rate and 44% had stable disease (with a median duration of 3.5 months).

Other agents that have been investigated in Phase II trials through the GOG include: trastuzumab (181B), thalidomide (229B), gefitinib (229C), lapatinib (229D), bevacizumab (229E), brivanib (229I), bevacizumab + temsirolimus (229G), and AZD6244 (229H). Bevacizumab was well tolerated and active based on PFS at 6 months (13.5% ORR and 40.4% PFS6) while the combination of temsirolimus and bevacizumab was active based on both objective tumor response and PFS at 6 months (24.5% ORR and 46.9% PFS 6) in recurrent or persistent EMC but was associated with significant toxicity (Aghajanian et al., 2011; Alvarez et al., 2012). Single agent trastuzumab failed to demonstrate significant activity in a phase II study in stage III/IV recurrent endometrial cancer (GOG-181B) (Roque et al. 2013) but a phase II study of carboplatin/paclitaxel with or without trastuzumab in patients with advanced or recurrent endometrial serous cancers confirmed to be HER2/Neu positive by immunohistochemistry or fluorescent in situ hybridization reported improved PFS (8 vs. 12.6 months, p=0.005) among patients treated with trastuzumab (Fader *et al,* 2018).

2.2 Investigational Agent

2.2.1 Avelumab

2.2.1.1 Investigational Agent Rationale

Avelumab (also referred to as MSB0010718C) is a human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. 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 (Chemnitz *et al.*, 2004; Keir *et al.*, 2008; Riley, 2009). 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; PD-L1 expression is greatly up-regulated after activation or interferon treatment (Keir *et al.*, 2008). 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 (Bennett et al., 2003; Blank et al., 2004; Blank et al., 2006; Brown et al., 2003; Dong et al., 1999; Freeman et al., 2000; Waeckerle-Men et al., 2007). In PD-1–/– mice both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies (Okazaki and Honjo, 2006, 2007). Breaking tolerance through, 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 (Blank et al., 2005). External (Okazaki and Honjo, 2007) and internal immunohistochemistry studies 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 (Brown *et al.*, 2003). 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 (Okazaki and Honjo, 2007). Importantly anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effect in combination therapy setting (Blank et al., 2004; Hirano et al., 2005; Iwai et al., 2002; Iwai et al., 2005; Nomi et al., 2007; Strome et al., 2003; Zhang et al., 2009).

Clinical Phase I/II trials with MoAbs targeting either PD-L1 or PD-1 have shown promising hints for clinical efficacy, i.e., objective tumor response in indications such as NSCLC, melanoma, and ovarian cancer (Brahmer et al., 2012; Hamid et al., 2013; Topalian et al., 2012). Avelumab has two main mechanisms of action for exerting its anti-tumor effects:
1. PD-L1 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, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.
2. Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 MoAb, avelumab has ADCC potential. Upon binding to PD-L1 on tumor cells and binding with their Fc part to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC. Therefore, blocking PD-L1 inhibitory mechanisms by interactions with not only PD-1 but also the other ligand, B7-1, avelumab offers unique therapeutic potential compared with MoAbs targeting PD-1.

2.2.1.2 Rationale for Dose Selection:

Dose selection was determined following review of the PK, PD, receptor occupancy, and preliminary clinical safety and efficacy data observed in the ongoing Phase I Trial EMR 100070-001.

2.2.1.3 Pharmacokinetics and Target Occupancy

Avelumab plasma levels leading to full TO on PBMCs resulted in tumor growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a PD marker for the ability of avelumab to act on its target and to show clinical activity.

Target occupancy on peripheral blood CD3+ T-cells was therefore investigated in human blood in vitro by flow cytometry after spiking of whole blood samples from 8 healthy volunteers with avelumab over a concentration range of 0.003-10 µg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 µg/mL ± 0.042 µg/mL and a plateau indicating at least 95% receptor occupancy was reached in all donor blood samples at 1 µg/mL.

PK profiles obtained during the dose escalation phase of Trial EMR 100070-001 were utilized to investigate whether this concentration of at least 1 µg/mL was achieved throughout the dosing interval. The median ± standard deviation trough concentration at the end of the first cycle after administration of the 10 mg/kg dose is 21 ± 12 µg/mL (n=283). This median trough concentration increases during the subsequent cycles to 25 ± 16 µg/mL (second cycle) (n=269), 27 ± 17 µg/mL (third) (n=202), and remains between 27 and 36 µg/mL during the subsequent cycles (n=55–171).

These data were confirmed in ex-vivo samples taken at minimum trough concentration (Cmin) after

the first dose (Day 15) in a small number of subjects during the initial dose escalation part of the Phase Ib Trial EMR 100070-001 (n=9). For doses of 10 mg/kg, TO for 4 subjects was greater than 90%, at trough serum levels ranging between 12.69 to 26.87 μg/mL. Also for doses of 3 mg/kg available TO data for 2 subjects with trough levels ranging from 4.56 to 6.99 μg/mL, showed greater than 90% TO at trough exposure levels. At dose level 1 mg/kg, 2 out of 3 subjects displayed less than 90% TO at trough serum concentrations. Avelumab serum concentrations were below the quantification limit of 0.2 μg/mL in these 2 subjects.

Further evidence for a full TO achieved with the 10 mg/kg dose throughout the entire dosing interval was derived from the population PK model based on data of 410 subjects from ongoing studies EMR 100070-001 and EMR 100070-002. Eighty-three subjects with rich PK profiles, 9 subjects with peak and trough concentrations and 318 subjects with only trough concentrations were included in this analysis. A two compartment model with mixed linear plus Michaelis-Menten elimination was evaluated. Limited by very few observations collected in low concentration range showing non-linear elimination, a Michaelis-Menten elimination was only observed at very low concentrations (Vmax [maximal elimination]=0.07 mg/h [Relative standard error (RSE)=94%], Michaelis-Menten constant [KM]=0.9 μg/mL [RSE=448%]).

Based on these results, it can be assumed that at doses of 10 mg/kg and greater, administered every 2 weeks, a high TO is achieved in subjects throughout the entire dose interval.

2.2.1.4 Clinical Safety Data Related to Dose

As of the safety cutoff date of 01 June 2015, 770 subjects have received at least one dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, and were followed for at least 4 weeks. Overall, 717 subjects have received the proposed dose of 10 mg/kg in the expansion cohorts, of which 184 subjects have NSCLC, 120 subjects have gastric cancer, 75 subjects have ovarian cancer and 44 subjects have urothelial carcinoma.

In the dose escalation portion of the Trial EMR 100070-001, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the SMC suggests an acceptable safety profile of avelumab administered at the 10 mg/kg every 2 weeks dose and schedule. 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 TEAE was infusion-related reaction reported in 134 subjects (18.7%), followed by fatigue reported in 130 subjects (18.1%) and nausea reported in 74 subjects (10.3%). Grade ≥ 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. Infusion-related reactions including hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

2.2.1.5 Clinical Efficacy Data Related to PK

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 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 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 this pre-planned interim analysis on this 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).

A descriptive analysis was performed for the NSCLC expansion cohort to explore whether there was any correlation between the efficacy readouts and exposure as measured by Cmin after the first (Day 15) or second dose (Day 29) of avelumab administration. These analyses were separately performed with the 2 sets of Cmin data: Cmin after the first dose on Day 15 and Cmin after the second dose on Day 29. The analysis set consisted of all treated subjects (at least one fully administered dose within 80% to 120% of the intended dose) from the NSCLC expansion cohort for which preliminary trough PK concentrations (Cmin) and efficacy data were available (n=158 for Day 15 and n=143 for Day 29). Splitting the NSCLC subject cohort into categories characterized by unconfirmed Best Overall Response according to RECIST 1.1 (non-evaluable, progressive disease, stable disease [SD], PR, CR) showed no difference in median and distribution of the drug exposure between these cohorts as measured by Cmin. Moreover, there was no correlation between Cmin data on Day 15 or Day 29 and tumor response as measured by percent change from baseline to best post-baseline assessment achieved throughout the trial ($r2 < 0.01$ for both analyses using Day 15 and Day 29 PK data).

Based on these data, tumor response was not related to the drug concentrations at the end of the dosing interval.

Based on the PK results and the receptor occupancy data, sufficient trough concentrations appear to be achieved for full TO in the blood in all subjects receiving the 10 mg/kg dose. At the doses of 10 and 20 mg/kg, no target mediated drug disposition was observed in PK and population PK analyses, indicating a high receptor occupation at the end of the dosing interval. Within the dose range of 1 mg/kg to 20 mg/kg, AE data were not dose dependent resulting in no clear signaling that lowering the dose below 10 mg/kg would improve or enhance subject safety. Within the subject cohort receiving 10 mg/kg every 2 weeks to treat NSCLC, the efficacy parameters were not correlated with the achieved drug concentrations.

Based on these data, a dose of 10 mg/kg once every 2 weeks is considered the biologically optimal dose and was selected for further evaluation of avelumab in NSCLC subjects. The dose of 10 mg/kg once every 2 weeks is considered to have a favorable risk benefit profile and thus represents an appropriate dose for further evaluation in ongoing and planned avelumab trials.

2.2.1.6 Nonclinical Pharmacology:

An overview of pharmacology studies with avelumab is presented in Table 1 and Table 2.

Table 1 Overview of In Vitro Pharmacology Studies with Avelumab

Main Study ID	Individual Study ID	GLP-Status	Lot #	Assay	Readout	Main Results/Findings
	EMDL010 0019322	Non-GLP	A10-329-12	FACS was used to detect binding to PD-L1 expressing human tumor cell lines (A431, A549, BxPC3, HCT116, M24, PC3mm2, U-87 MG) with and without IFN-γ treatment	Histograms generated from FACS data.	Binding was clearly detected on all tested cell lines. IFN-γ pre-treatment increased PD-L1 expression on all tested cell lines.
IONC-CMI-04052011DZ	EMDL010 0018572	Non-GLP	A10-260-8	FACS was used to detect binding to human PBMC stimulated with PHA.	Histograms generated from FACS data.	Binding was clearly detected.
	EMDL010 0017432 EMDL010 0018269 EMDL010 0016741	Non-GLP	A10-329-12	FACS was used to measure dose-dependent binding to HEK293 cells engineered to express human PD-L1, murine PD-L1 or cynomolgus monkey PD-L1	Mean Fluorescence Intensity as measured by FACS.	Dose-dependent binding was observed to the PD-L1 of all three tested species. EC_{50} of 0.30 nM against human, 0.34 nM against murine, and 0.94 nM against cynomolgus monkey.
	EMDL010 0015527	Non-GLP	A09-098-3	OT-1 transgenic T cells were co-cultured with PD-L1-expressing EL4 cells that were pulsed with the SIINFEKL peptide in the presence of various concentrations of MSB0010608H	IFN-γ concentrations in culture supernatant were measured as an indicator of antigen-specific T cell activation.	T cell activation was significantly enhanced with an EC_{50} of 0.28 nM.
	EMDL010 0018294 EMDL010 0018293	Non-GLP	A10-260-9 A10-329-12	Human PBMC were stimulated with the SEA super-antigen in the presence of various concentrations of avelumab	IL-2 concentrations in culture supernatants were measured as an indicator of T cell activation.	T cell activation was significantly enhanced with an EC_{50} of 0.08 nM.

Main Study ID	Individual Study ID	GLP-Status	Lot #	Assay	Readout	Main Results/Findings
NBE-PDCR	PEAT2013 1213VS	Non-GLP	A09-273-2	Surface plasmon resonance was used to measure binding to PD-L1 and various other B7 family members (i.e., PD-L2, PD-1, B7.1, B7-H2, B7-H3	Binding constants were determined from the measured surface Plasmon resonance signal using Biacore technology	Binding was selective for PD-L1 versus the other B7 family members tested.
NBE-PDCR	EMDL010 0014796 EMDL010 0015405 EMDL010 0015407 EMDL010 0019379 EMDL010 0019665	Non-GLP	A10-260-5	Biacore Kinetic Assay was used to compare standard binding kinetic profiles of avelumab to various lots of human, cyno, murine, dog, rat and rabbit PDL-1 analytes	Immobilized goat anti human IgG Fc antibody captured the anti hu PDL-1 F02 antibody at 10 nM and the analyte at 100, 50, 25, 12.5 and 0 nM were tested for binding.	Avelumab has KD to human PD-L1 of 0.7 nM. Affinities to mouse and monkey PD-L1 was found to be very similar, while the affinity to dog PD-L1 was within ten-fold lower, to rat and rabbit PD-L1 was about 100 and 150-fold reduced as compared with human PD-L1.
NBE-PDCR	EMDL010 0019119 EMDL010 0019120 EMDL010 0019123 EMDL010 0019124	Non-GLP	A10-260-5	Chromium release was used in the ADCC assay to detect cell lysis of PD- L1 expressing human tumor cells (A431 and A549) with and without pre IFN-g treatment.	Titration curves of percent lysis vs antibody concentration were generated from the assay.	Multiple repeat assays with the same donor effector cells and from multiple donors with different FcRIIIa polymorphism. Avelumab was demonstrated to be ADCC competent with effector cells containing the FcRIIIa VV and VF polymorphism against PD-L1 expressing tumor cells.

Main Study ID	Individual Study ID	GLP-Status	Lot #	Assay	Readout	Main Results/Findings
NBE-PDCR	EMDL010 0019467 EMDL010 0019468	Non-GLP	A10-260-5	Chromium release was used in the CDC assay to detect cell lysis of PD- L1 expressing human tumor cells (A431, A549 and M21).	Titration curves of percent lysis vs antibody concentration were generated from the assay.	Avelumab was demonstrated to be CDC incompetent against PD-L1 expressing tumor cells. Notably, under the condition tested, the lysis mediated by Cetuximab was negative while complement activity was confirmed by 14.18-IL2 lysis of M21 cells.
NBE-PDCR	DAF00012 DAF00013	Non-GLP	A10-329-12, A10-260-9	Competition assay measuring the ability of avelumab to block the binding of radiolabeled ^{125}I-PD-L1 to immobilized PD-1.	Percentage of specific binding in the presence of various concentrations of avelumab.	The PD-L1/PD-1 interaction was potently inhibited with an IC_{50} of 0.071 nM.
IONC090120 13DZ	DZH00028 DZH00025	Non-GLP	VPD Z810 2 PDZ C003 A11-121-6	PD-L1 on CD3 T cells in isolated cynomolgus and human PBMC treated with various concentrations of avelumab was detected by flow cytometry using biotinylated avelumab.	The % TO of a given sample can be calculated by the formula: (1 - unbound PD-L1/overall level of PD-L1) × 100%.	The estimated concentrations of avelumab required to saturate 50% of PD-L1 on cynomolgus monkey and human CD3 T cells are 0.04 and 0.02 µg/mL, respectively.
IONC190920 14SM	n.a.	Non-GLP	PDZ C003	PD-L1 on CD3 T cells in human whole blood from 8 donors treated with various concentrations of avelumab was detected by flow cytometry using biotinylated avelumab.	The % TO of a given sample can be calculated by the formula: (1 - unbound PD-L1/overall level of PD-L1) × 100%.	The estimated concentrations of avelumab required to saturate 50% of PD-L1 on CD3 T cells are 0.122 µg/mL ± 0.042 µg/mL. Near-complete TO at >1 µg/mL for all donors.

ADCC: antibody-dependent cell-mediated cytotoxicity; EC_{50}: effective concentration exerting 50% effect; FACS: fluorescence-activated cell sorting; Fc: fragment crystalline; GLP: good laboratory practice; IC_{50}: concentration exerting 50% inhibition; IFN-γ: interferon-gamma; IgG: immunoglobulin G; IL-2: interleukin-2; KD: affinity constant; n.a: not applicable; PBMC: peripheral blood mononuclear cell; PD-1: programmed death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; PHA: phytohemagglutinin; SEA: staphylococcal enterotoxin A; TO: target occupancy.

Table 2 Overview of In Vivo Pharmacology Studies with Avelumab

Main Study ID	Individual Study ID	GLP-Status	Lot #	Species/Model/ Group Size	Doses/Treatment Schedule	Main Results/Findings
IONC20042 011AKH	TI10-050	Non-GLP	A10-260-10	Mouse/MC38 colon carcinoma/ n=10	Avelumab 100, 200, 400, or 800 µg i.v. bolus every 3rd day for 3 total administrations	Significant inhibition of tumor growth with a trend toward dose-dependent activity.
	TI10-070	Non-GLP	A10-260-10	Mouse/MC38 colon carcinoma/ n=14	Avelumab 100, 200, 400, or 800 µg i.v. bolus every 3rd day for 3 total administrations	Significant inhibition of tumor growth with a trend toward dose-dependent activity.
IONC20042 011BKH	TI10-078	Non-GLP	A10-260-9	Mouse/PANC02 pancreatic adenocarcinoma/ n=10	Avelumab 400 µg i.v. on Days 8, 11,14 Gemcitabine 300 mg/kg i.v. on Days 5, 19, 26	Combination treatment significantly increased survival time.
	TI11-002	Non-GLP	A10-260-9	Mouse/PANC02 pancreatic adenocarcinoma/ n=10	Avelumab 400 µg i.v. on Days 8, 11, & 14 Gemcitabine 300 mg/kg i.v. on Days 5, 19, 26	Combination treatment significantly increased survival time.
	TI11-003	Non-GLP	A10-260-9	Mouse/PANC02 pancreatic adenocarcinoma/ n=10	Avelumab 400 µg i.v. on Days 13, 16, 19 Gemcitabine 150 mg/kg i.v. on Days 5, 12, 26, 33	Combination treatment significantly increased survival time.
IONC20042 012CKH	TI10-079	Non-GLP	A10-260-10	Mouse/MC38 colon carcinoma/ n=10	Avelumab 400 µg i.p. on Days 3, 6, 9 Oxaliplatin 5mg/kg i.p. on Days 0,14 5-fluorouracil 60 mg/kg i.v. on Days 0 and 14	Combination treatment had an approximately additive effect. Avelumab treatment increased $CD8^+PD\text{-}1+$ T cells and increased effector memory $CD8^+$ T cells.

	TI11-001	Non-GLP	A10-260-10	Mouse/MC38 colon carcinoma/ n=10	Avelumab 400 µg i.p. on Days 3, 6, 9 Oxaliplatin 5mg/kg i.p. on Days 0,14 5-fluorouracil 60 mg/kg i.v. on Days 0 and 14	Combination treatment had an approximately additive effect. Avelumab treatment increased $CD8^+PD\text{-}1+$ T cells and increased effector memory $CD8^+$ T cells.
IONC10032 011RT	TI10-072	Non-GLP	A10-260-9	Mouse/MC38 colon carcinoma/ n=10	Avelumab 400 µg i.v. on Days 3,6,9 Local radiation 360 cGy on Days 0,1,2,3,4	Combination showed synergistic anti-tumor activity that achieved complete tumor regression in 6 out of 10 mice.
	TI11-006	Non-GLP	A10-260-5 A10-260-6	Mouse/MC38 colon carcinoma/ n=8	Avelumab 400 µg i.v. on Days 3,6,9 Local radiation 360 cGy on Days 0,1,2,3,4 Weekly administration of anti-CD8 antibody to deplete $CD8^+$ T cells	Combination showed synergistic anti-tumor activity. Depletion of $CD8^+$ T cells negated combination effect. Increased tumor antigen-specific $CD8^+$ T cells and effector memory $CD8^+$ T cells. Increased proliferation of $CD8^+$ T cells.
IONC11032 011RT	TI10-039	Non-GLP	A10-031-3	Mouse/MC38 colon carcinoma/ n=8	MSB0010294 400 µg i.p. Every 3rd day for 3 total administrations Weekly administration of anti-CD8 antibody to deplete $CD8^+$ T cells	Depletion of $CD8^+$ T cells completely abrogated the efficacy of avelumab, confirming that the mechanism of action is primarily $CD8^+$ T cell driven.
IONC08062 012RT	TI11-017	Non-GLP	A10-260-5 A10-260-15	Mouse/MC38 colon carcinoma/ n=10	Avelumab 200 or 400 µg (glycosylated & deglycosylated forms) i.v. bolus every 3rd day for 3 total administrations Weekly administration of anti-ASGM1 to deplete NK cells	Enzymatically deglycosylated antibody showed significantly reduced anti-tumor activity. Similar reduction in efficacy observed following systemic NK cell depletion. Suggests ADCC activity contributes to in vivo efficacy.

ADCC: antibody-dependent cell-mediated cytotoxicity; GLP: good laboratory practice; i.p.: intraperitoneal; i.v.: intravenous; NK: natural killer.

2.2.1.7 Nonclinical Pharmacokinetics:

The PK of avelumab was evaluated in mice and cynomolgus monkeys after single IV administration. Additional PK data were obtained during the course of repeated dose toxicity studies. These studies are summarized in Table 3.

Table 3 Overview of Results of Nonclinical Pharmacokinetic Studies with Avelumab

Type of Study (Study Number)	Lot#	Species/ Group Size	Dose (mg/kg)	Treatment Duration	Major Findings
Pharmacokinetics/Single Dose					
B-09-009	A08-274-1	Balb/c mice n=3	0.4, 4, and 20	i.v. single dose	Non-linear pharmacokinetics with lower clearance at higher doses. Two different elimination phases: accelerated clearance was noted once plasma concentration declines below around 10 µg/mL
TI11-051 B-11-033	A10-329-12	C57BL/6 mice n=20	25, 50, 100, 200, 200 µg/mouse	i.v. single dose	Non-linear pharmacokinetics with lower clearance at higher doses. Dose-dependent duration of target occupancy. Target occupancy depends on plasma concentration. 50% target occupancy at 12 days after the 400 µg dose.
RF2120	A10-134-4	Cynomolgus monkeys n=3 (male)	0.8, 4 and 20	i.v. single dose	The exposure increased dose-proportionally between low and intermediate dose. Lower clearance at the high dose leading to higher exposure. Anti-drug antibodies affected exposure in some animals.
Toxicokinetics/Repeated Dose					
RF2740	A10-260-13	CD-1 mice n=6 (3 female; 3 male)	0, 20, 40 and 140	Once weekly for 5 consecutive weeks by i.v. injection	The exposure increased approximately in proportion to the dose. No accumulation was observed after repeated dosing. No gender differences were observed.
RF3310	A10-329-12	Wistar Han Rats n=6 (3 female; 3 male)	0, 20, 40 and 140	Once weekly for 5 consecutive weeks by i.v. injection	The exposure increased approximately in proportion to the dose. Accumulation: in peak and trough levels (up to 200 %) at all dose levels was noted in the majority of the animals. No gender differences were observed.
RF2710	A10-329-12	Cynomolgus monkey n=4 (2 female, 2 male)	0, 20, 60 and 140	Once weekly for 5 consecutive weeks by i.v. infusion (1.5 h)	The exposure increased approximately in proportion to the dose. No gender differences were observed.
RF4990	S148/211007 /P1/DS S148/L1 S148/211017 /P1/DS S148/L4	Cynomolgus monkey n=10 (5 female, 5 male) for 0 mg/kg and 140 mg/kg dose group n=6 (3 female, 3 male for 20 mg/kg and 60 mg/kg dose groups	0, 20, 60 and 140	Once weekly for 13 consecutive weeks by i.v. infusion (1.5 h)	The exposure increased roughly in proportion to the dose at the intermediate dose and slightly more than in proportion to the dose at the high dose. Moderate accumulation after repeated dosing was observed. No gender differences were noted. No immunogenicity was observed.

i.v.: intravenous.

2.2.1.8 Toxicology:

The toxicological profile of avelumab was evaluated in repeat dose toxicity studies of 4-week duration with weekly IV bolus injection/infusion in mice, rats and cynomolgus monkeys (Studies RF2710, RF2740, RF4990, RF3310, and T16228). An additional repeat dose toxicity study with intermittent once weekly IV infusion over 13 weeks followed by an 8-week recovery period was performed in cynomolgus monkeys (Study RF4990). Investigations on the local tolerability were integrated in the repeat-dose toxicity studies.

The repeat-dose rodent studies were performed under non-Good Laboratory Practice (GLP) conditions and the studies with cynomolgus monkeys were conducted according to GLP. In addition, an in vitro cytokine release assay in human and cynomolgus monkey whole blood and PBMCs was performed (non-GLP; StudiesT17985, T17986, and 14-DA471-N0) as well as a TCR study in normal human and cynomolgus monkey tissues according to GLP (Study 20015186 and Study20015187).

The non-GLP studies were conducted according to quality management system standard in order to ensure quality and data integrity.

An overview of the toxicology studies performed with avelumab and major findings is provided in Table 4.

Table 4 Overview of Toxicology Studies with Avelumab

Type of Study	Species/Strain/ Study #	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Status	Noteworthy Findings
Safety Pharmacology (in vivo)						
Monkey, Cynomolgus/ RF2710[b]		i.v. infusion (once weekly)	4 weeks	20, 60, 140	Yes	There were no apparent test article related effect on heart rate, arterial blood pressure, duration of the heart rate corrected QT intervals, respiratory rate, body temperature, or CNS function.
Monkey, Cynomolgus/ RF4990		i.v. infusion (once weekly)	13 weeks	20, 60, 140	Yes	There were no relevant effects on cardiovascular function, in particular the duration of the heart rate corrected QT interval of the ECG, respiratory rate, CNS function and rectal temperature.
Single-Dose Toxicology Studies – None performed						
Repeat-Dose Toxicology Studies						
Mouse, CD-1/RF2740		i.v. bolus (once weekly)	4 weeks	20, 40, 140	No	Mortality was observed at all dose levels. The mortality rate was higher in the low dose group and death occurred within 30 minutes mainly after the 3rd weekly injection. The observed clinical symptoms before their death as well as the histopathological findings (immunocomplex deposition) suggest hypersensitivity reactions in mice.
Mouse, CD-1/T16228		i.v. bolus (once weekly)	4 weeks	20	No	Clinical findings and mortality observed in Study RF2740 were confirmed. Due to very limited and hemolytic blood volumes, the planned investigations of clinical chemistry, immunogenicity, and cytokine parameters could not be performed.
Rat, Wistar Han/RF3310		i.v. bolus (once weekly)	4 weeks	20, 40, 140	No	Slight and multifocal increase in the grade of severity of mononuclear cell infiltrates and of sinusoidal lining cells in the liver in both genders of the control group and all dose groups. These changes represent well-known background findings in the liver, with the dose groups being slightly more affected compared to the control. Although no dose-dependency was visible, a relation to treatment cannot be excluded. Under the conditions of the present study, avelumab was systemically and locally tolerated up to 140 mg/kg.

Type of Study	Species/Strain/ Study #	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Status	Noteworthy Findings
Repeat-dose toxicity (continued)						
Monkey, Cynomolgus/ RF2710[b]		i.v. infusion (once weekly)	4 weeks	20, 60, 140	Yes	Systemically well tolerated up to and including the high dose of 140 mg/kg. There were no signs of systemic toxicity either at the in vivo and post-mortem investigations. At the i.v. injection site, an increased severity of subcutaneous/perivascular and vascular inflammatory and degenerative changes (including necrosis), was seen in monkeys given 140 mg/kg.
Monkey, Cynomolgus/ RF4990		i.v. infusion (once weekly)	13 weeks	20, 60, 140	Yes	Systemically well tolerated up to and including the high dose of 140 mg/kg. There were no signs of systemic toxicity either at the in vivo and post-mortem investigations. Treatment-related changes were seen at the injection sites; subcutaneous fibroplasia and mononuclear cell infiltrates were slightly, but not dose-dependently, enhanced in animals of the treated groups compared to controls, possibly as a consequence of locally infiltrated test item. All histological changes were completely reversible after an 8-week recovery. No relevant effects on cytokine parameters and no evidence of ADA.
Genotoxicity - Not planned; not required and not appropriate for biologics (ICH S6 and S9 guidelines)						
Carcinogenicity - Not planned; not required and not appropriate for biologics (ICH S6 and S9 guidelines)						
Reproductive and developmental toxicity – Not planned; given the known role of PD-1/PD-L1 in maintaining the maternal/fetal tolerance, avelumab can be expected to have an adverse effect on pregnancy, including embryo-lethality. A warning of such risks will be considered as part of the product information						
Local tolerance - Evaluated within repeat-dose studies						

Type of Study	Species/Strain/ Study #	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Status	Noteworthy Findings
Other Toxicology Studies						
Repeat-dose study	Mouse CD-1/IONC-T112-003RVT	i.v. bolus (once weekly)	2 or 3 weeks	5, 20	No	Sensitization and challenge with avelumab induced an anaphylaxis-like reaction including severely reduced activity levels and severe drops in body temperature as well as acute lethality within 15-90 minutes after the treatment in 64% of the mice. Sensitization with avelumab and challenge with the inactive control antibody showed comparable effects on activity levels and body temperature, and death occurred in 21% of the mice. Pre-treatment with PAF or serotonin/histamine inhibitors revealed significant protection from decreases in activity levels and body temperature and the number of lethal events was also reduced. Inhibition of PAF was considerably more effective than of serotonin/histamine, suggesting that the IgG pathway is more strongly involved than the IgE pathway.
Cytokine release in human and cynomolgus PBMCs	Human and cynomolgus PBMCs/ T17986	in vitro	24 hours	0.0001, 0.001, 0.01, 0.1, 1, 10, 100 nM	No	Only minor effects of MSN0010718C were seen in human and cynomolgus PBMCs: In pooled human PBMCs only a minimal effect was seen after 6h exposure to avelumab (3 fold increase in TNF alpha in male non pre-stimulated cells). However, after 24h a more significant and robust increase in TNF alpha release was observed in both male and female derived PBMCs (at concentrations at and above 0.1 nM). Pre-stimulation with SEA caused a complete loss of this effect. After 6h female cynomolgus PBMCs showed small increases in IL6 and MCP-1. The release of these cytokines was increased after 24h. In male cynomolgus PBMCs little was observed after 6h, but after 24h small increases in IL2, IL6 and IL8 were observed. In both sexes the pre-stimulation with SEA caused a small increase in IFN-γ, in addition to those seen with no pre-stimulation.

Type of Study	Species/Strain/ Study #	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Status	Noteworthy Findings
Other Toxicology Studies (continued)						
Cytokine release in human and cynomolgus whole blood	Human and cynomolgus whole blood/ T17985	in vitro	24 hours	0.0001, 0.001, 0.01, 0.1, 1, 10, 100 nM	No	Weak and sporadic response seen in individual human donor whole blood suggest that avelumab has little potential to induce an inflammatory reaction: After 6h, IL8 was slightly increased in both male and female whole blood. After 24h IL8 was still increased in multiple donors, but IL6, IL1 beta and IFN gamma were also increased in several donors. These effects were minimal, with the exception of 2 female donors who showed a severe induction of IL6 release. In cynomolgus, there are hints that an immune response can be triggered, but only at higher concentrations: After 6h in female cynomolgus whole blood pool only around 2-fold increases in IL6, IL8 and TNF alpha release were seen. Larger increases in the release of these same cytokines (plus IL1 beta) were seen in male cynomolgus whole blood – but only at one concentration. Again, after 24h, only small effects were seen in female cynomolgus whole blood, although a slightly increased release was seen compared to 6h (IFN gamma, IL8 and IL6). In male cynomolgus whole blood the highest concentration of avelumab caused a large increase in TNF alpha and IL1beta. Smaller increases in IL6, IL8 and IFN gamma were also observed.
Cytokine Release Assay	Human/14-DA471-N0	In vitro	6 hours, 24 hours	0.0139, 0.06952, 0.13104, 0.6952, 1.3904, 6.952, 13.904 nM	No	In this optimized cytokine release assay, avelumab caused a strong increase in multiple cytokines (e.g. IL6, MCP-1 and TNF-alpha) in PBMCs derived from all 16 human donors tested. In activated PBMCs from female donors the major response was observed in IL6 and TGF-beta and in male donors a different profile was obtained in that alongside the IL6/TGF-beta response, both GM-CSF and IL10 were induced. In addition, the pharmacodynamic marker, MCP1, was also induced in most, but not all donors. A stronger MCP1 release was observed in PBMCs obtained from female donors when compared to male donors. Weaker and sporadic increases in IL8 and IL1-beta were also observed in both sexes. There were very few differences in the cytokine release profile between avelumab manufactured using processes A or B. When differences were observed the greatest induced release of specific cytokines was mostly seen for avelumab manufactured using process A.

Type of Study	Species/Strain/ Study #	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Status	Noteworthy Findings
Other Toxicology Studies (continued)						
Human TCR study	Human tissues/20015186	in vitro	n.a.	n.a.	Yes	Staining was observed in the following tissues: Plasma membrane only in the following tissue elements: adipocytes in the adrenal, heart, lymph node, and ovary. Plasma membrane and cytoplasm in the following tissue elements: epithelium in the adrenal (cortex), bladder (mucosa), breast (ducts, glands), colon (mucosa), eye (cornea, conjunctiva), Fallopian tube (mucosa), gastrointestinal (GI) tract (esophagus [mucosa, glands, ducts], small intestine [mucosa], and stomach [mucosa]), kidney (parietal cells, tubules), liver (hepatocytes, bile ducts), lung (bronchioles, alveoli [including type I and type II pneumocytes]), ovary (surface), pancreas (acini, ducts), parathyroid, pituitary (including Rathke's pouch), placenta (amnion, trophoblasts), prostate, salivary gland (ducts, acini), skin (epidermis, hair follicles, sweat glands, sebaceous glands), thymus (epithelial-reticular cells), thyroid (follicles), tonsil (surface, crypts), ureter (mucosa), and uterus (cervix [mucosa] and endometrium [endometrial surface, glands]). Mesothelium in the colon, Fallopian tube, heart, lung, spleen, and testis. Mononuclear leucocytes in the GI tract (esophagus), heart, and lymph node. Alveolar macrophages in the lung. Smooth myocytes in the bladder, colon, GI tract (esophagus and small intestine), prostate, and ureter. Islet cells in the pancreas, parafollicular (C) cells in the thyroid, decidual cells in the placenta, granulosa cells in the ovary, interstitial cells in the testis. Cytoplasm only in the following tissue elements: epithelium in the eye (lens) and testis (germinal), endothelium in the bladder, GI tract (esophagus), lymph node, spleen, thymus, tonsil, and uterus (endometrium). Mononuclear leukocytes in the skin and tonsil. Reticulo-endothelial cells in the spleen, smooth myocytes in the stomach, placenta, spleen, testis, and uterus (endometrium) and megakaryocytes in the bone marrow. Neurofilaments/neural cell processes in the gray and white matter of the brain (cerebellum and cerebral cortex) and spinal cord, plexi of the colon and small intestine, retina of the eye, and neurohypophysis of the pituitary. Axons of spinal nerve roots in the spinal cord and intravascular and/or leaked serum in the majority of human tissues.

Type of Study	Species/Strain/ Study #	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Status	Noteworthy Findings
Other Toxicology Studies (continued)						
Cynomolgus monkey TCR study	Monkey tissues/20015187	in vitro	n.a.	n.a.	Yes	Overall, less staining was observed with avelumab in the cynomolgus monkey tissue panel compared to the staining patterns observed in the human tissue panel in the companion human tissue cross-reactivity study (Study No. 20015186). In human tissue panel, staining of adipocytes, megakaryoytes, ovarian granulosa cells, testicular interstitial cells, and serum was present with avelumab; however, staining of these tissue elements was not observed in the cynomolgus monkey tissues. There was staining of neural cell processes in human CNS tissues which were most likely of astrocytic (glial) origin, which correlates with staining of astrocytes in cynomolgus monkey CNS tissues. Additionally, avelumab stained ovarian stromal cells and oocytes in the cynomolgus monkey tissues, but not in the human tissue panel. However, minimal oocytes were present in the human ovaries examined. The reasons for the observed differences in staining between the human and cynomolgus monkey were not determined but might include section to section variation, differences in donor age and/or disease status, dying processes, or other unidentified differences. Except for these differences, avelumab staining of human and cynomolgus tissues was comparable.
UV Absorption profile (phototoxicity)	n.a./ 50238	(UV absorption)	n.a.	n.a.	No	The UV-VIS spectrum has a maximum of absorbance around 280 nm that decreases to reach zero at 307.4 nm. No absorption was observed in the range from 307 to 700 nm. The maximum of the peak is at 278.09 nm (A=0.75), this band is due to the aromatic residues of the protein, and has a weak shoulder around 282 nm. Below 250 nm the absorption increases steadily up to 227.09 nm and then decreases towards shorter wavelengths. The extinction coefficient was: 1.46 mL mg-1 cm-1

ADA: anti-drug antibody; CNS: central nervous system; ECG: electrocardiogram; GI: gastrointestinal; GLP: Good Laboratory Practice; GM-CSF: granulocyte macrophage colony-stimulating factor; IFN-γ: interferon-gamma; IgE: immunoglobulin E; IgG: immunoglobulin G; IL: interleukin; i.v.: intravenous; MCP-1: monocyte chemotactic protein-1; n.a.: not applicable; NOAEL: no observed adverse effect level; PBMC: peripheral blood mononuclear cell; SEA: staphylococcal enterotoxin A; TCR: tissue cross reactivity; TGF: transforming growth factor; TNF: tumor necrosis factor.

[a] For repeat-dose toxicity, the highest systemic NOAEL is underlined.

[b] The bioanalytical measurements, multi analyte profiling, blood immunophenotyping, toxicokinetics and immunogenicity data analysis were not conducted in GLP compliance, but in accordance to MSR-QMS.

2.2.1.9 Toxicology Summary:

The toxicological profile of avelumab was investigated in vivo in mice, rats, and cynomolgus monkeys (Studies RF2710, RF2740, RF4990, RF3310, and T16228). In addition, an in vitro cytokine release assay in human and cynomolgus monkey whole blood and PBMCs (Studies T17985, T17986, and 14-DA471-N0) as well as a TCR study in normal human and cynomolgus monkey tissues was performed (Study20015186 and Study20015187).

On the basis on the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. However, in the repeat dose-toxicity studies in CD-1 mice with avelumab IV bolus injection mortality occurred mainly after the 3rd administration. A mechanistic study supported the hypothesis that the mortalities are caused by an

immune-mediated hypersensitivity reaction, the mechanism of which is highly likely to be anaphylaxis (immunoglobulin E [IgE]/IgG mediated reaction). Due to severe hypersensitivity reactions after repeated administration in mice and the low binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) is envisaged.

Accordingly, repeat dose-toxicity studies of 4 and 13 weeks duration have been conducted in cynomolgus monkeys. Neither in the pilot 4-week IV repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity have been seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week IV repeat-dose toxicity study, a NOAEL of 140 mg/kg for systemic toxicity was established. Available toxicokinetic data in monkeys showed a t1/2 of 60 to 70 hours and linear kinetics of avelumab in this species.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in PHA pre-stimulated PBMCs. Clinical experience has demonstrated that the relative risk of an infusion reaction is low (approximately 2%) and with premedication drops to a very low level (less than 1%) indicating that the optimized CRA substantially overestimates the risk of cytokine release in a clinical setting.

2.2.1.10 Interactions:
No formal drug interaction trials have been conducted with avelumab in humans.

2.2.2 Talazoparib

2.2.2.1 Investigational Agent Rationale

Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers.

As of 30 November 2016, approximately 439 patients have received talazoparib in company-sponsored studies in hematologic malignancies and solid tumors. Studies in solid tumors include a Phase 1 study (PRP-001) in advanced or recurrent solid tumors, a Phase 1 study in advanced malignancies (PRP-002), a Phase 2 study (673-201) in locally advanced and/or metastatic breast cancer patients with a germline BRCA defect, a Phase 3 study (673-301) in locally advanced or metastatic breast cancer with a germline BRCA defect, a Phase 1 hepatic impairment study (MDV3800-02), a Phase 1 absorption, distribution, metabolism and excretion (ADME) study (MDV3800-03), and a Phase 1 study on cardiac repolarization (MDV3800-14). As of 30 November 2016, aggregate safety data from 3 company-sponsored clinical studies evaluating talazoparib monotherapy at the proposed dose of 1 mg QD in patients with advanced malignancies (Phase 1 studies PRP-001 and MDV3800-14 and Phase 2 study 673-201; 164 patients total) provide the basis for the most common TEAEs. The most common TEAEs associated with talazoparib (>20%) occurring in patients who received 1 mg QD talazoparib were anemia (42.1%), fatigue (36.6%), nausea (29.3%), thrombocytopenia (25.6%), neutropenia (20.7%), and alopecia (20.1%). The most common Grade 3 or higher drug-related TEAEs occurring in ≥5% of patients were anemia (28.0%), thrombocytopenia (16.5%), and neutropenia (12.2%).

Serious AEs (SAEs) occurred in 52 of 164 patients (31.7%) who received 1 mg QD talazoparib. SAEs occurring in ≥2% of patients were pleural effusion (4.3%), anemia and dyspnea (3.7% each), and neoplasm progression and thrombocytopenia (2.4% each). Fourteen patients had SAEs considered related to talazoparib, which included anemia (3.0%); thrombocytopenia (2.4%); platelet count decreased (1.2%); and increased transaminases, neutropenic sepsis, and vomiting (0.6% each).

A total of 12 of 164 patients (18.8%) who received 1 mg QD talazoparib had a TEAE that led to death (6 associated with the underlying malignancy including 1 also associated with bronchopneumonia; 2 dyspnea; and 1 each disease progression, lung infection, hypoxia, and respiratory failure). Of these events, none were assessed as related to talazoparib.

Among the 164 patients who received 1 mg QD talazoparib, 19.5% had a TEAE that led to dose reduction and 57.3% had a TEAE that led to dose interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression.

Five of 164 patients (3.0%) treated with talazoparib at a dose of 1 mg QD permanently discontinued talazoparib due to a TEAE. The TEAEs that led to study drug discontinuation were anemia, increased ALT, increased AST, metastatic breast cancer, and dyspnea.

In the ongoing Phase 3 study 673-301, 308 patients with locally advanced or metastatic breast cancer were treated as of the cutoff date. An estimated 206 patients were receiving talazoparib and 102 were receiving another single-agent chemotherapy of physician's choice, based on the 2:1 randomization scheme. A serious TEAE of veno-occlusive disease of the liver leading to death was assessed as related to talazoparib by the Investigator in a 34-year old female patient with advanced breast cancer metastatic to the axilla and bone who developed asymptomatic Grade 3 liver test abnormalities (ALT and AST with normal bilirubin) while receiving talazoparib at 0.75 mg. Ten days after talazoparib dosing was discontinued due to Grade 4 thrombocytopenia, the patient had acute hepatic failure attributed to veno-occlusive disease of the liver by the Investigator. The Sponsor considered veno-occlusive disease of the liver an unlikely etiology, a consideration supported by 2 independent hepatologists who reviewed the case.

Clinical Efficacy in Patients with Advanced Solid Tumors

A total of 110 patients with advanced tumors with DNA repair pathway abnormalities, particularly those associated with BRCA and phosphatase tensin homolog (PTEN) dysfunction, were enrolled in the Phase 1 study PRP-001, which was completed in March 2015. The maximum tolerated dose (MTD) of talazoparib was defined as 1 mg QD and it was used in the expansion phase of the study in patients with breast, ovarian/primary peritoneal, and pancreatic cancer with deleterious germline mutations; small cell lung cancer (SCLC); and Ewing sarcoma. As of 13 February 2015, the proportion of patients with breast, ovarian/primary peritoneal, and pancreatic cancers with BRCA mutations who were treated with talazoparib at 1 mg QD and had objective responses according to RECIST v1.1 was 50% (7 of 14; 95% CI: 23.0, 77.0), 41.7% (5 of 12; 95% CI: 15.2, 72.3), and 20.0% (2 of 10), respectively. Cancer patients harboring BRCA mutations who are resistant to platinum-based chemotherapy display decreased sensitivity to PARP inhibitors.19 Given the exploratory nature of Cohort F, pancreatic cancer patients in this cohort will

not include patients who progressed within 6 months of starting previous platinum-based chemotherapy. This is aligned with the approach followed for other indications in this study. Responses were also reported in 2 patients with SCLC (8.7%; 2 of 23; 95% CI: 1.1, 28.0).

2.2.2.2 Rationale for Dose Selection

The dose levels of talazoparib to be evaluated in this study are supported by clinical studies in patients with advanced malignancies. In the PRP-001 Phase 1 study in patients with advanced or recurrent solid tumors, talazoparib was escalated from 0.025 to 1.1 mg QD and the recommended dose for further development was determined to be 1 mg QD. Data from that study at 1 mg/day demonstrated objective responses or clinical benefit (CR, PR, or SD

≥24 weeks) in patients with breast, ovarian/peritoneal, pancreatic cancer, SCLC, and Ewing sarcoma. The dose level of 1 mg QD is currently being used in the ongoing randomized Phase 3 study 673-301 in patients with locally advanced or metastatic breast cancer.

2.2.2.3 Pharmacokinetics and Target Occupancy

The PK of talazoparib as a single agent was evaluated in 142 adult patients with cancer, including 109 patients with solid tumors (Study PRP-001) and 33 with hematologic malignancies (Study PRP-002). Doses of 0.025 mg to 2 mg were administered orally as a single dose or as QD doses. This dose range bracketed the 1 mg QD dose used in ongoing safety and efficacy studies, and provided a framework for assessing dose linearity. As the PK of talazoparib was similar in patients with solid tumors and hematologic malignancies, and no differences were apparent between males and females, the results are summarized collectively. Oral absorption of talazoparib was rapid and independent of dose after administration of single or QD doses. Peak talazoparib concentrations were generally reached approximately 1 to 8 hours post-dose. Exposure increased approximately dose-proportionally with increasing doses. At 1 mg/day, the mean t1/2 was approximately 2 days; the mean apparent volume of distribution (V/F) was 415 L, indicating extensive extravascular distribution. Steady state was reached in approximately 2 to 3 weeks with daily administration. Apparent oral clearance (CL/F) of talazoparib appeared to be dose linear, with a mean CL/F across doses of approximately 5 L/h. Renal excretion was a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44% to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady state for doses up to 1 mg QD.

Mean renal clearance ranged from 1.38 L/h to 4.96 L/h independent of dose, suggesting linear urinary elimination kinetics. Following repeated administration at 1 mg QD, talazoparib accumulated approximately 2.4-fold relative to a single dose.

At steady state, the mean maximum plasma concentration (Cmax) was 21.0 ng/mL (55 nM), the mean plasma trough concentration (Ctrough) was 3.72 ng/mL (9.87 nM), and the mean area under the plasma concentration-time curve (AUC) was 202 ng*h/mL (532 nM*h). The Ctrough of talazoparib at steady state at 1 mg QD is above the Ctrough values at the efficacious dose of 0.33 mg/kg daily used in some of the xenograft models (1.3 nM).

PK data from a food-effect study showed that food had no effect on the extent of absorption of talazoparib (AUC) but decreased the rate of absorption (Cmax was 46% lower and time to Cmax [Tmax] was 2.63 hours later); however, this reduction in the rate of absorption following a single dose is not clinically relevant because talazoparib accumulates 2.4-fold at steady state after 1 mg QD dosing. Furthermore, AUC or Ctrough is thought to drive efficacy, not Cmax; therefore, talazoparib can be taken with or without food. Talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

A preliminary population PK analysis used data from patients in Studies PRP-001 and PRP-002 to assess the effects of renal function on the PK of talazoparib. The talazoparib CL/F in patients with mild renal impairment (creatinine clearance [CLCR] 60-89 mL/min) was similar compared with patients with normal renal function (CLCR ≥90 mL/min**).** In patients with moderate renal impairment (CLCR 30-59 mL/min), the talazoparib CL/F was decreased by 44% from normal, resulting in higher talazoparib exposure. The talazoparib starting dose for patients with moderate renal impairment is discussed in Section 1.2.6.2. The effect of renal impairment on talazoparib PK is also being investigated in the ongoing study MDV3800-01.

The effect of hepatic impairment on talazoparib PK is being investigated in the ongoing MDV3800-02 study.

The potential for talazoparib to affect the PK of other drugs was assessed through in vitro experiments and described in the talazoparib IB (Investigator's Brochure of talazoparib (MDV3800, BMN673), dated 07 Jul 2017.).

2.2.2.4 Clinical Safety Data Related to Dose

Based on preliminary population PK analysis from patients in Studies PRP-001 and PRP-002, the talazoparib CL/F was decreased by 44% from normal in patients with moderate renal impairment (CL_{CR} 30-59 mL/min), and therefore in those patients the 1 mg QD talazoparib starting dose should be reduced to 0.75 mg QD, as discussed in the talazoparib IB (Investigator's Brochure of talazoparib (MDV3800, BMN673), dated 07 Jul 2017). In the Phase 1b portion of this study, only patients with a creatinine clearance of ≥60 mL/min (as estimated using the Cockcroft-Gault formula) will be eligible for enrollment. The entirety of the available clinical data, including data from the ongoing study MDV3800-01 in patients with renal impairment when available, at the conclusion of the Phase 1b portion will be used to determine the appropriate starting dose for talazoparib in Phase 2 portion in patients with moderate renal impairment.

Since avelumab is an immunoglobulin (Ig)G1 mAb eliminated by intracellular lysosomal proteolytic degradation throughout the entire body while talazoparib is a small molecule cleared primarily via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation, no PK DDI is anticipated between avelumab and talazoparib when given in combination. Nevertheless, concentration-time data will be measured on this study for both avelumab and talazoparib following coadministration at single dose and at steady state, and will be compared with historical PK data for avelumab and talazoparib as single agents.

2.2.2.5 Interactions

No formal drug interaction trials have been conducted with talazoparib in humans.

2.2.3 Axitinib

2.2.3.1 Rationale for Axitinib

Abnormal vasculature is a hallmark of solid tumors, including gynecologic cancers. Tumor-related blood vessels are irregular secondary to disordered, immature growth stimulated by VEGF as well as by physical intra- and peri-tumoral compression by cancer cells, fibroblasts, and components of the extracellular matrix. Abnormal vasculature contributes to a hypoxic state, leading to a cascade of tumor-survival changes, including induction of epithelial-mesenchymal transition pathways, promotion of a cancer "stem cell" phenotype, switch to anaerobic metabolism, and generation of an immunosuppressive microenvironment (Jain et al, 2014). Therefore, much work has been focused on modifying tumor vasculature to thwart these changes, and in parallel, improve intratumoral delivery of chemotherapy or immunotherapy.

Axitinib is a small molecule inhibitor that binds to the catalytic domain of non-activated (non-phosphorylated) receptor tyrosine kinase. It is a highly potent inhibitor of VEGF receptors 1, 2, and 3 (VEGFR1-3).

2.2.3.2 Preclinical efficacy

Axitinib is a highly potent inhibitor of VEGFR 1, 2 and 3, with IC_{50} of approximately 0.09, 0.2, and 0.1-0.29nM respectively. Axitinib had weaker inhibitory activity against PDGF receptor α (PDGFRα), PDGFRβ, and KIT, with respective IC_{50} values of 5.0, 1.6, and 1. nM.

In vitro, axitinib inhibited VEGF-mediated endothelial cell adhesion and migration and induced endothelial cell apoptosis within 6 hours of treatment of cell cultures. Anti-angiogenic activity was demonstrated in several xenograft tumor models, in which axitinib treatment led to reduced tumor microvessel density, tumor blood flow/permeability, tumor cell proliferation, and was associated with increased tumor apoptosis (Axitinib Investigator's Brochure). These effects were similarly seen in murine models of spontaneous pancreatic islet-cell tumors and lung carcinomas: axitinib decreased endothelial cell fenestrations, vascular sprouting, patency, blood flow, and VEGFR2/3 expression. Single agent axitinib was effective in orthotopic murine models of colon and lung carcinomas, RCC, and HCC, with maximum tumor growth inhibition (TGI) of 96%, 75%, 74%, and 54% respectively.

2.2.3.3 Clinical Pharmacokinetics

As of June 2018, 45 studies evaluate the safety, efficacy, and PK of axitinib were completed or were ongoing, including 15 Phase I studies involving 532 healthy subjects (inclusive of one study in participants with hepatic impairment) and 30 studies encompassing 3016 cancer patients receiving axitinib monotherapy (n=1824) or in combination (n=1192).

In humans, the plasma pharmacokinetics of axitinib at steady state were generally linear. Axitinib is rapidly absorbed with maximal plasma concentrations occurring within 4 hours of oral

administration. Mean absolute bioavailability (in healthy volunteers) was 58%. Axitinib administered at 5mg orally achieved a maximal plasma concentration (C_{max}) of 32 ng/mL with $t_{1/2}$ of 5.2 hours.

Metabolism of axitinib occurs primarily through the CYP3A4 enzyme, and to a lesser extent by the CYP1A2, CYP2C19, and UGT1A1 enzymes as determined from in vitro studies. Axitinib elimination occurs through hepatobiliary excretion; renal excretion does not contribute to elimination of axitinib. Axitinib was evaluated in subjects with hepatic impairment, finding that plasma pharmacokinetics of a single dose of axitinib were not altered in those with mild hepatic impairment (Child Pugh Class A). However, there was a 2-fold increase in AUC_{inf} and a 1.3-fold increase in C_{max} in subjects with moderate hepatic impairment (Child Pugh Class B). A Phase II study in patients with HCC suggested that no dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child Pugh Class A), but that the starting dose of axitinib can be reduced by approximately half (to 2mg BID) in those with moderate hepatic impairment (Child Pugh Class B). Axitinib has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

No significant difference in axitinib clearance was seen in patients with mild to severe renal impairment (CrCl 15-89 mL/min), suggesting that no dose adjustment is needed for patients with mild to severe renal impairment.

Axitinib plasma pharmacokinetics were not statistically different when studied in Caucasian, Chinese, and Japanese subjects.

A food effect study evaluating crystal polymorph Form XLI of axitinib determined that there was no clinically meaningful food-effect for Form XLI FCIR tablets.

2.2.3.4 Clinical Safety

In patients with solid tumors treated with single agent axitinib in the first-in-human (FIH) trial, 10 of 10 subjects in the first cohorts developed hypertension, with 5 of Grade 3 or 4 severity. Hypertension was responsive to antihypertensive medications and resolved with cessation of axitinib treatment. Two participants had seizures that may have been associated with hypertension, one receiving 20mg BID and the other receiving 10mg BID. In subsequent cohorts in which patients received doses <20mg BID, hypertension was a DLT in 1 of 6 patients receiving 15mg once daily. Zero of 14 patients receiving axitinib 5mg BID had hypertension that could not be managed with standard antihypertensive medications. In the second cohort of the FIH study, 1 patient with NSCLC developed fatal hemoptysis that was considered related to axitinib. Other bleeding events in the other 36 participants were epistaxis, breast hemorrhage, hematochezia, rectal hemorrhage, and vaginal hemorrhage, all Grade 1 and considered unrelated to axitinib.

Fourteen patients were ultimately treated at the MTD within the FIH trial. Of these patients, one patient experienced a DLT of Grade 2 stomatitis, one experienced a DLT of Grade 3 diarrhea, and 6 patients experienced Grade 1-3 hypertension that was not dose limiting and was managed with standard antihypertensive medications.

For single agent axitinib, pooled safety data from FIH and Phase I-III trials (1474 cancer patients)

showed the most common treatment-emergent all-causality AEs were diarrhea 55%, hypertension 51%, fatigue 47.1%, decreased appetite 40%, nausea 32.6%, decreased weight 32.3%, dysphonia 31.1%, palmar-plantar erythryodysesthesia syndrome 29.4%, hypothyroidism and vomiting 22.6%, constipation 20.3%, proteinuria 20.1%. The most frequent Grade ≥3 AEs were hypertension 20.7%, fatigue 10.2%, and diarrhea 10.1%. The most frequent Grade 3 or 4 hematologic abnormalities were lymphocytes 8.8%, hemoglobin 2.4%, and neutrophils 1.5%. The most frequent Grade 3 or 4 laboratory abnormalities were lipase 8.9%, hyponatremia 7.4%, hyperkalemia 5.1%, hyperglycemia 4.8%, hypophosphatemia 4.7%, amylase 4.3%, AST 4.1%, ALT 3.4%, hypokalemia 2.5%, hypocalcemia 1.7%, and total bilirubin 2.3%.

2.2.3.5 Clinical efficacy

Single agent axitinib demonstrated early evidence of clinical efficacy in Phase II trials across NSCLC (Schiller et al 2009), radioactive iodine-refractory thyroid cancer (Cohen et al, 2008), melanoma (Axitinib Investigator's Brochure), and metastatic RCC (Rixe et al 2007).

A subsequent Phase III trial of single agent axitinib in previously-treated advanced RCC demonstrated higher ORR compared to sorafenib (19.4% vs 9.4%, p=0.0001) and improved median PFS compared (6.7 mo vs 4.7 mo, p<0.0001) (Motzer et al 2013), however there was no statistically significant improvement in median OS (20.1mo vs 19.2mo, p=0.374). Similarly, in treatment-naïve advanced RCC, single agent axitinib led to higher ORR compared to sorafenib (32% vs 15%, p=0.0006) and improved median PFS (10.1 mo vs 6.5 mo, p=0.038), without improvement in median OS (21.7 mo vs 23.3 mo, p-0.4883) (Hutson et al, 2017). Overall, this data suggested that single agent axitinib was not sufficient to produce a meaningful difference in overall survival, and that combination strategies may be needed.

2.3 Rationale

2.3.1 Rationale for avelumab alone

It has been suggested that tumors with higher mutational load may harbor more tumor-specific neoantigens that may lead to increased tumor-infiltrating lymphocytes (TILs) (Rooney et al., 2015). In this regard, recent analyses of TCGA data have implicated neoantigen load in driving T cell responses(Brown et al., 2014) and have identified novel associations between specific genomic alterations and increased immune infiltrates in various tumors(Hussein et al., 2015; Rajasagi et al., 2014; Rutledge et al., 2013). Furthermore, high mutational loads have been associated with high neoantigen loads and an elevated number of TILs which is counterbalanced by overexpression of immune checkpoints (Hussein et al., 2015; Llosa et al., 2014; Xiao and Freeman, 2015). The Cancer Genome Atlas project identified 2 groups of endometrioid endometrial cancers (ECs) with high mutation frequency: an ultramutated group (7% of all tumors) that harbored mutations in the exonuclease domain of polymerase e (POLE), and a hypermutated group (28% of tumors) with microsatellite instability (MSI), the majority of which harbored MLH1 promoter methylation. It has recently been demonstrated that POLE and MSI ECs are associated with significantly increased predicted neoepitopes and numbers of CD3+ and CD8+ TILs compared with microsatellite stable (MSS) tumors (Howitt et al., 2015). Specifically, POLE mutated endometrial tumors had almost 15-fold higher predicted neoantigen load compared to MSI tumors (two-sided t-test, p<0.001) and MSI tumors had an almost 7-fold higher median number of predicted neoepitopes per sample than MSS

tumors (two-sided t-test, $p<0.001$) (Howitt et al., 2015). Furthermore, PD-1 was significantly overexpressed in TILs and peritumoral lymphocytes of POLE and MSI compared with MSS ECs suggesting that POLE and MSI tumors may be excellent candidates for immunotherapies targeting the PD-1 pathway (Howitt et al., 2015; van Gool et al., 2015).

Furthermore, the anti-PD-1 antibody pembrolizumab has demonstrated very promising activity in mismatch repair deficient colorectal and non-colorectal cancers (Le et al., 2015). Specifically, the immune-related objective response rate and immune-related progression-free survival rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair–deficient colorectal cancers; the median progression-free survival and overall survival were not reached in the cohort with mismatch repair–deficient colorectal cancer. Patients with mismatch repair–deficient noncolorectal cancer had responses similar to those of patients with mismatch repair–deficient colorectal cancer (immune-related objective response rate, 71% [5 of 7 patients]; immune-related progression-free survival rate, 67% [4 of 6 patients]).

Finally, although in the study published in JAMA Oncology (Howitt et al. 2015) MSS tumors were in average associated with lower neoantigen load, lower number of tumor infiltrating lymphocytes (TILs) and lower expression of PD-1 and PD-L1 compared to POLE-mutated and MSI-tumors, it is important to underscore that a sizeable fraction of MSS tumors exhibited a high number of TILs, and high expression of PD-1 and PD-L1. Specifically:

- 34% of MSS tumors were associated with presence of peritumoral CD3+ T-cells in the stroma surrounding the epithelial component
- 28% of MSS tumors were associated with expression of PD-1 in intraepithelial lymphocytes
- 28% of MSS tumors were associated with expression of PD-1 in peritumoral lymphocytes
- 13% of MSS tumors were associated with PD-L1 expression in intraepithelial immune cells
- 19% of MSS tumors were associated with PD-L1 expression in tumors cells and
- 56% of MSS tumors were associated with PD-L1 expression in peritumoral immune cells.

Based on these data, although we expect that MSS endometrial tumors will be less responsive to PD-L1 inhibition than POLE and MSI endometrial cancers, our data support that a sizeable fraction of MSS tumors may also respond to PD-L1 blockade. Therefore, we include a cohort of patients with MSS tumors to specifically address the question of whether these tumors may also respond to PD-L1 blockade.

2.3.2 Rationale for avelumab in combination with talazoparib

2.3.2.1 MSS cohort did not respond to single agent avelumab

The preliminary results for this phase II two-stage study of avelumab revealed that among the 16 patients enrolled in the MSS cohort, 14 patients developed progressive disease. One patient had confirmed partial response and one patient had irRECIST PFS6 but not RECIST PFS6. Given these results a second stage was not warranted for this cohort. (Konstantinopoulos, et al; results presented at SGO 2018 Meeting, New Orleans, LA)

However, based on the mechanisms of action discussed above, talazoparib and avelumab have the potential to produce additive or synergistic anti-tumor activity, with talazoparib functioning to promote immune priming and tumor immunogenicity and avelumab functioning to overcome PD-L1-mediated inhibition of any resulting anti-tumor immune response.

2.3.2.2 Some endometrial cancers exhibit homologous recombination deficiency and respond to PARP inhibition

There is a growing body of evidence that PARP inhibitors may have efficacy in a variety of tumors with homologous recombination (HRR) defects, including a subset of endometroid endometrial adenocarcinomas. (Reinbolt, *et al*, 2013) A recent case report A 42-year-old woman with a germline *BRCA2* mutation and recurrent low-grade endometrioid endometrial adenocarcinoma experienced clinical and radiographic response to the PARP inhibitor, olaparib. This patient remains in clinical remission after 15+ months of treatment. (Gockley, *et al*; 2018)

Deficiency of the tumor suppressor gene *PTEN* is associated with homologous recombination defects similar to *BRCA* mutations. When exposed to PARP inhibitors, *PTEN* deficient cells suffer synthetic lethality similar to the mechanism triggered in *BRCA*-deficient cells treated with PARP inhibitors. (Mendes-Pereira, A.M., *et al.,* 2009) In ovarian cancer, a focal deletion region at 10q23.31 that includes only PTEN has been found in approximately 7% of HGSOCs. These tumors exhibit homozygous PTEN deletion which is also associated with downregulation of PTEN at the mRNA level. (TCGA, 2011) PTEN deficiency has been shown to be synthetically lethal with PARP inhibition or compound PARP-PI3K inhibition (Dedes, K.J., *et al*.,2010 and Bian, X., *et al.,* 2017), and one of the proposed mechanisms is transcriptional downregulation of RAD51 (Mendes- Pereira, A.M., *et al.,* 2009 and Bian, X., *et al.,* 2017). Specifically, in an *in-vitro* study, deficiency of the tumor suppressor *PTEN* in endometrioid endometrial cancer cell lines was associated with increased sensitivity to olaparib. (Dedes, K.J., *et al.,* 2010) Furthermore, in a case report of a 58-year-old woman who presented with metastatic endometrioid endometrial adenocarcinoma and had several platinum-sensitive relapses, olaparib treatment (as part of a phase 1 trial) was associated with significant reduction in the size of her brain metastases and subjective improvement in her symptoms after 10 weeks. At 8 months the patient had progression of her tumor and a biopsy at that time revealed intact somatic *BRCA 1* and *2* but a loss of *PTEN*. (Forster, *et al.,* 2011) However, another study showed that *PTEN* deficient endometrioid endometrial cancer cells are not responsive to PARP inhibitor olaparib monotherapy, but instead show superior sensitivity to compound inhibition with the PI3K inhibitor BKM120. (Bian, X., *et al.,* 2017) These apparently conflicting data indicate that the association of *PTEN* deficiency with HRR deficiency and response to PARP-inhibitors is likely context-specific. However, these studies suggest that further investigation into this area is likely to identify which patients with gynecologic malignancies may benefit from PARP inhibition.

2.3.2.3 PARP inhibitors may induce immune priming for response to immune checkpoint inhibitors

Since the activity of avelumab depends on generation of a productive immune response, composed of effective antigen presentation, T-cell priming, infiltration of tumors, and recognition and killing of tumor cells (Chen, et al., 2013) Talazoparib, via its ability to promote increased

DNA damage, has the potential to promote several of these key stages of the immune response. Figure 1

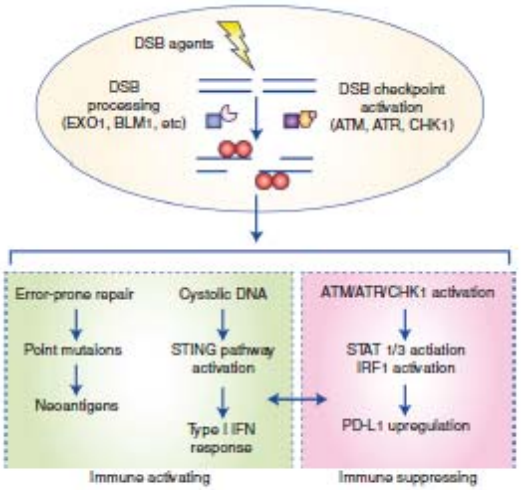


Fig. 1 Immune activating and suppressive effects of DNA double-strand break (DSB) signalling. DSBs created by damaging agents such as ionizing radiation activate a network of signalling pathways that balance the host immune response. If repaired using an error-prone pathway such as non-homologous end joining (NHEJ) or alternative end joining, DSBs can result in somatic mutations that act as neoantigens. DNA damage can also activate the innate immune system via the STING pathway.[15] DSB-mediated immune activation is balanced by concomitant inhibitory signalling, including upregulation of PD-L1 expression. Sato et al. show that DNA damage signalling via the checkpoint kinases ATM, ATR, and Chk1 drive PD-L1 expression on tumour cells via STAT1/STAT3/IRF3 activation

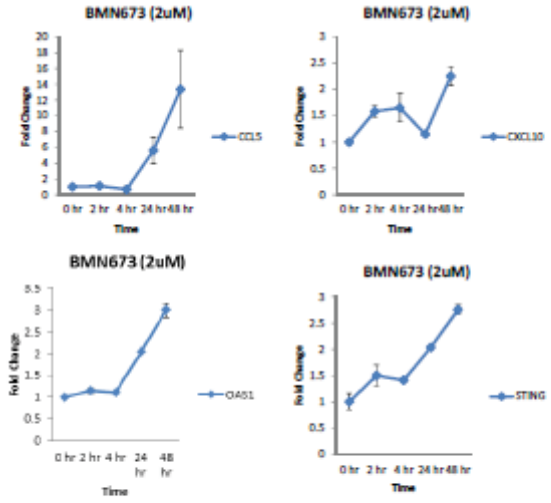
Firstly, talazoparib-mediated cell death, via either PARP trapping or via increased DNA damage, has the potential to release antigens into the tumor microenvironment, promoting effective antigen presentation; this has been described for other therapies that lead to increased tumor cell death (Galluzi, et al., 2017). Secondly, DNA damage promotes inflammation via two alternative pathways, the first being activation of the NF-κB pathway via ataxia-telangiectasia mutated (ATM)-mediated phosphorylation of the NF-κB essential modulator (NEMO) (Ioannidou, et al., 2016) and the second being activation of the STING pathway via generation and detection of cytosolic DNA (Hartlova, et al., 2015 and Parkes, et al., 2016). Activation of these pathways leads to increased pro-inflammatory signaling that enhances effective recognition and infiltration of tumors by immune cells, and has recently been shown to be critical to the response to checkpoint inhibition in mice (Wang, et al., 2017). Finally, DNA damage has been shown to lead to up-regulation of MHC, NKG2DL, and ICOSL, (Soriani, et al., 2009 and Tang, et al, 2014). which would be expected to increase the intrinsic immunogenicity of tumor cells and enhance their recognition and killing by T cells and NK cells.

In keeping with these critical links between DNA damage and immune priming, talazoparib has been shown to drive the activation of STING and downstream target genes in cultured cell lines (Figure 2) and to promote T cell and NK cell infiltration and activation in a mouse model of ovarian cancer (Huang, et al., 2015).

However, talazoparib treatment has also been shown to lead to 2-3 fold increased expression of PD-L1 by tumor cells,18 suggesting that this may represent a mechanism of resistance to possible talazoparib-mediated anti-tumor immunity, and suggesting that the combination of talazoparib and anti-PD-L1 may further enhance anti-tumor activity. This hypothesis is

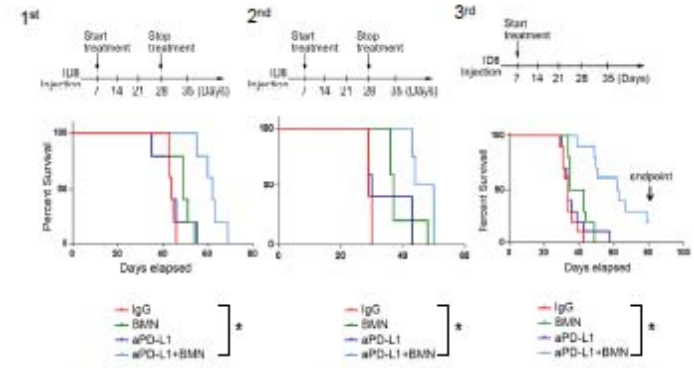
supported by preclinical studies in syngeneic mouse models of ovarian (Figure 3) and colorectal cancer, which demonstrate a significant improvement in overall survival (OS) in mice treated with the combination of talazoparib and an anti-mouse PD-L1, but not in mice treated with either talazoparib or anti-mouse PD-L1 alone.

Figure 2: Analysis of the STING Pathway Downstream Target Induction by Talazoparib (BMN 673)



Using ovarian cancer cell line HOC1, RNA expression was analyzed for the major downstream targets of the STING pathway, C-C Motif Chemokine Ligand 5 (CCL5), C-X-C motif chemokine 10 (CXCL10) and 2-5-Oligoadenylate Synthetase 1 (OAS1). STING expression was also analyzed. Following incubation with BMN 673 (2 μM) over 48 hours, fold increase in mRNA expression of these proteins was assessed by RT-PCR analysis.

Figure 3: Combination of Talazoparib (BMN 673) and Anit-mouse PDL-1 Treatment Significantly Prolongs Survival in an Ovarian Cancer Model



Survival curves from 3 independent experiments comparing the combination of BMN 673 (0.33 mg/kg daily by oral gavage) and anti-PD-L1 (200 μg/mouse every 3 days) to talazoparib alone, anti-PD-L1 alone, or IgG control. In the left and middle panels, mice were treated for 3 weeks and treatment was stopped to monitor survival of the mice. In the right panel, mice were treated continuously until the mice met criteria for euthanasia and survival was monitored. Statistical analysis was conducted by log rank test. The combination treatment significantly improved mouse survival compared to IgG control in three experiments ($p < 0.01$).

2.3.2.4 Evidence of PARP inhibitor/PD-1/PDL-1 inhibitor combined efficacy

Prior studies have suggested that the combination of PD-L1 blockade and PARP inhibition may lead to tumor inhibition. The combination of olaparib with durvalumab was evaluated in a Phase 1/2 study in 10 patients with metastatic castration resistant prostate cancer. Overall, 8 out of 10 patients

had a reduction in PSA level, including 5 patients who had declines in PSA level ≥50% from baseline. PSA level reductions were observed in patients with bone-only disease, in those who had bone disease and soft-tissue or visceral metastases, and in patients with or without mutations in DNA repair pathways (Karzai FH, et al.,2017).

While prior work suggests that PARP inhibitors alone have limited activity outside of BRCA mutations with a reported ORR of ~ 5% in *BRCA* wild type patients (Gelmon, et al. 2011), new work suggests that this limitation may be overcome with addition of PD-1 blockade. In the ovarian cancer cohort of the TOPACIO/Keynote -162 study, platinum resistant ovarian cancer patients with up to 5 prior lines of chemotherapy were treated pembrolizumab (anti-PD-1) and niraparib (PARP inhibitor) combination therapy and a 25% ORR was observed. When this cohort was evaluated across biomarker populations, *BRCA* mutated patients had a 25% ORR, but interestingly, encouraging ORR was seen among HRD positive patients (25%) as well as wild-type *BRCA* (24%) and HRD negative patients (27%). This study suggests that platinum resistant ovarian cancer patients may benefit from the combination of PD-1 blockade/PARP inhibition regardless of their *BRCA* or HRD status. (Konstantinopoulos, et al; presented at the 2018 ASCO Annual Meeting, Chicago, IL)

Importantly, in order to limit patient exposure to an inactive agent, our study follows a two-stage design that allows for early stopping for futility.

Based on the above data, this trial will interrogate the activity and toxicity of avelumab and talazoparib in a second cohort of MSS patients based on initial study which suggested that single agent avelumab was ineffective in these patients.

2.3.3 **Rationale for avelumab in combination with axitinib**

Single agent axitinib is insufficient for meaningful clinical response
As noted in Section 2.2, single agent axitinib yielded an improvement in median PFS but did not improve median overall survival in either the front-line or subsequent treatment of advanced renal cell carcinoma, suggesting that relying on anti-VEGFR as the sole mechanism of antitumor activity is insufficient.

Disordered tumor vasculature promotes immune suppression
The vasculature of solid tumors is abnormal morphologically, with disordered growth and inefficient vessel branches, and functionally, with leaky vessel walls. These abnormal blood vessels are further compressed by tumor cells, fibroblasts, and tumor stroma, leading to reduced delivery of drugs, disease-directed therapies, and immune cells. The hypoxic environment promotes an overall immunosuppressive state, predominantly mediated by HIF1 α. HIF1α attracts myeloid-derived suppressor cells (MDSC) and promotes their differentiation into tumor-associated macrophages, which in turn suppress T cells (Corzo et al 2010; Doedens et al 2010), as well as attracting regulatory T cells (Tregs) into the tumor microenvironment (Clambey et al, 2012). This is compounded by HIF1α-mediated upregulation of inhibitory PD-L1 on myeloid derived suppressor cells, dendritic cells, and tumor cells (Noman et al 2014). VEGF, secreted by tumor cells either in response to HIF1α or through oncogene upregulation, also promotes an immunosuppressive environment by decreasing cytotoxic T cell trafficking and effector function, promoting MDSC expansion, promoting Treg proliferation and differentiation, and inhibiting the appropriate

maturation of antigen-presenting dendritic cells (Datta et al 2019; Jain et al 2014).

Therefore, by using ant-angiogenic agents to restore the tumor vasculature to a more normal morphology, distribution, and function, tumor perfusion can be improved. This has the effects of (1) enhancing delivery of oxygen, chemotherapeutics, and immune cells, thereby (2) reducing hypoxia and converting the immunosuppressive tumor microenvironment into an immunostimulatory one.

Preclinical efficacy of combination anti-angiogenic therapy and immune checkpoint blockade (CPB)

In murine models of melanoma, several studies using anti-VEGF therapy combined with a T-cell directed therapy led to increased anti-tumor activity compared to either agent alone and was associated with enhanced infiltration of T cells into tumors. Increased numbers of activated dendritic cells were seen, and conversely Tregs were decreased (Shrimali et al 2010; Li et al 2006). In a murine model of HCC, intratumor infiltration and activation of CD8+ T cells was only seen when anti-PD1 therapy was added to sorafenib and CXCR4 inhibition (Chen et al 2015). Similar effects were seen in murine models of breast cancer treated with VEGFR2 inhibition and a cancer vaccine, and in a murine model of colorectal cancer combining VEGF inhibition with a GM-CSF-secreting vaccine (Huang et al 2012; Li et al 2006). This preclinical suggested that combinations of anti-angiogenic therapies and immunotherapies may be promising.

Clinical efficacy of combination anti-angiogenic therapy and immune checkpoint blockade (CPB)

The combination of axitinib (anti-VEGFR1-3) and avelumab (anti-PD-L1) was studied first in the JAVELIN Renal 100 Phase 1b trial in advanced clear cell RCC. There was preliminary indication of clinical efficacy, with 32 of 55 (58%) treated patients demonstrating confirmed objective responses (Choueiri et al 2018). The MTD was established as axitinib 5mg BID with avelumab 10mg/kg every 2 weeks. One patient died due to treatment-related autoimmune myocarditis. Grade 3 or worse palmar-planter erythrodysesthesia, elevated ALT, elevated amylase, and elevated lipase were seen in 4 patients each (7%). Grade 3 or worse hypertension was seen in 16 patients (29%). This was followed by a randomized Phase III trial of combination avelumab/axitinib vs sunitinib, in previously treated advanced RCC (Motzer et al 2019). A total of 442 patients received avelumab 10mg/kg every 2 weeks + axitinib 5mg BID, compared to 444 patients who received sunitib. Among all-comers, avelumab/axitinib was associated with a median PFS of 13.8 months compared to 8.4 months with sunitinib, with HR 0.69 (CI 0.56-0.84, $p<0.001$); a confirmed ORR of 51.4% was seen with avelumab/axitinib compared to 25.7% with sunitinib. This benefit in all-comers was comparable to those with PD-L1 positive tumors (i.e. 63.2% of treated patients), in whom median PFS was 13.8 months with avelumab/axitinib compared to 7.2 months with sunitinib (HR 0.62, CI 0.47-0.79, $p<0.001$). In PD-L1 positive patients the confirmed ORR was 55.2% with avelumab/axitinib compared to 25.5% with sunitinib. At the time of data cutoff, patients were continuing to be followed for overall survival, though at a median follow-up for overall survival of 11.6 months and 10.7 months in the two treatment groups for PD-L1-positive patients, 37 patients and 44 patients had died, respectively. Based on these results, the combination of avelumab and axitinib was approved by the FDA in May 2019 for the first-line treatment of advanced RCC.

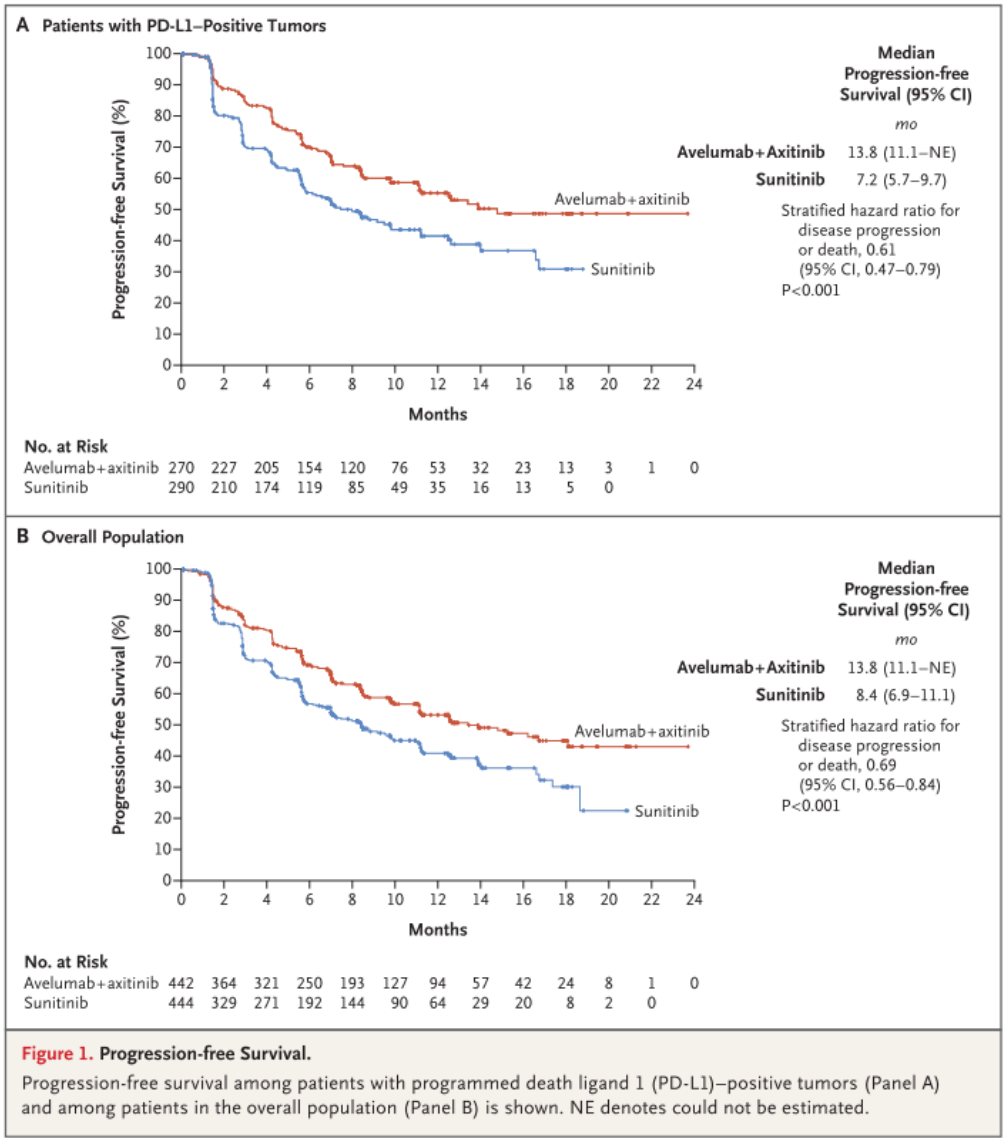
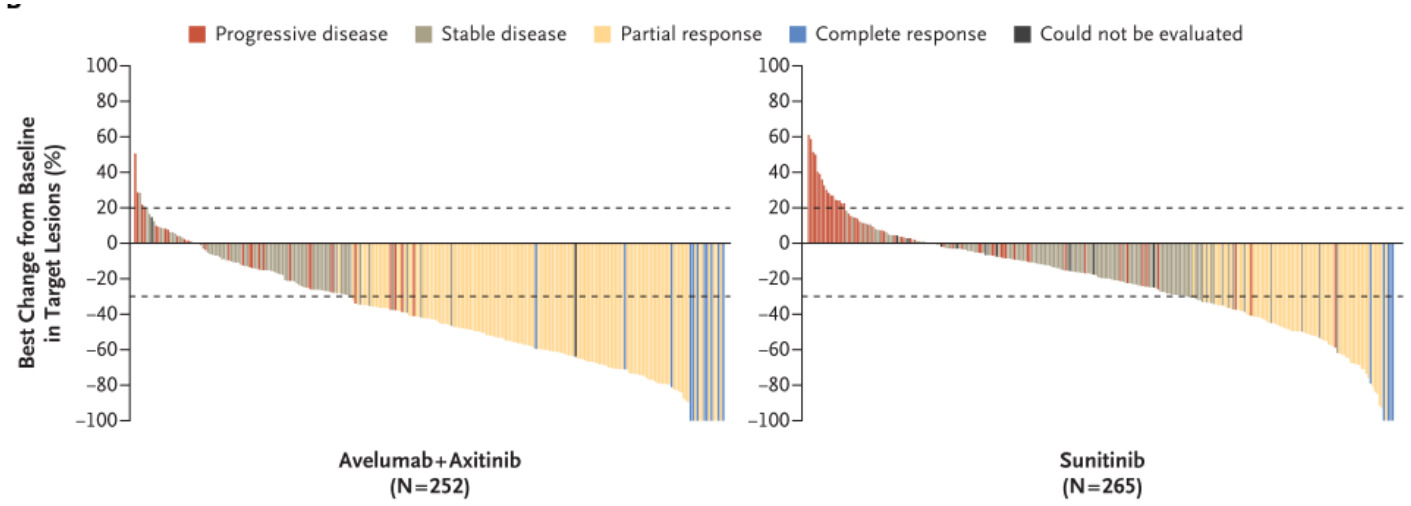


Figure 1. Progression-free Survival.
Progression-free survival among patients with programmed death ligand 1 (PD-L1)–positive tumors (Panel A) and among patients in the overall population (Panel B) is shown. NE denotes could not be estimated.



Results from Phase III trial of avelumab/axitinib vs sunitinib in RCC (Motzer et al 2019)

Given these encouraging results suggesting synergistic activity of dual antiangiogenic and immune CPB agents, a similar combination was recently studied in uterine cancer. Lenvatinib (a multikinase inhibitor of VEGFR1-3) and pembrolizumab (anti-PD-1 agent) were combined in a single arm Phase II trial of 53 patients with metastatic endometrial cancer, who notably were not selected for PD-L1 nor microsatellite status. Patients predominantly had serous histology (38%) and had received prior platinum doublet therapy (98%). Three patients (6%) had received prior bevacizumab (anti-VEGF). Thirteen patients (25%) were PD-L1 positive, 11 (21%) were negative, and 29 (55%) were unknown. Four patients (8%) were MSI-H, 45 (85%) were MSS, and 4 (8%) had unknown microsatellite status. The primary endpoint was proportion of patients with an objective response at week 24. At week 24, 21 of 54 patients (39.6%) had achieved an objective response by investigator review; by independent review 24 patients (45.3%) had achieved an objective response at week 24. The best overall response by independent review was CR in 3 patients (5.7%), PR in 22 patients (41.5%), and SD in 19 patients (35.8%). Eleven patients achieved responses lasting at least 6 months, and 8 patients achieved responses lasting at least 12 months. The estimated median PFS was 7.4 months in the per-protocol population.

Based on the above data, and based on a previous cohort in this protocol showing low activity of single agent avelumab in MSS endometrial cancer (ORR 6.3%), a new cohort evaluating combination avelumab/axitinib in MSS endometrial cancer will determine whether addition of anti-VEGFR activity will enhance immune CPB in this population.

2.4 Correlative Studies Background

The identification of predictive correlates to response to treatment with checkpoint blockade has proven a critical, but elusive goal, with numerous proposed approaches across different tumor types, but none that has thus far gained widespread clinical acceptance (Ascierto, 2013; Herbst *et al.*, 2014). Several efforts have focused on the identification of PD-L1 expression via immunohistochemistry (IHC) on the surface of tumor, or infiltrating immune cells. Some studies have suggested a significant correlation between tumoral PD-L1 expression and response in non-small cell lung cancer (Garon *et al.*, 2015), although others utilizing a similar approach have failed to identify a significant correlation (Borghaei *et al.*, 2015; Brahmer *et al.*, 2015). Notable challenges in this strategy include the lack of standardization among IHC assays, the use of differential thresholds for assay positivity and a lack of consensus regarding the importance of explicitly accounting for PD-L1 expression on infiltrating immune cells. Complicating the development of these approaches are concerns that inadequate negative predictive value and full understanding of the underlying immune dynamics between the host and tumor may result in the exclusion of patients who may benefit from treatment.

For this trial we will characterize PD-L1 and PD-L2 expression on tumor cells and infiltrating immune cells in baseline formalin fixed paraffin embedded (FFPE) blocks of cancer tissue (which are required for eligibility) and in optional biopsy specimens where available in conjunction with the Dana-Farber Cancer Institute Center for Immunooncology. We will also characterize CD3+ T-cells, CD8+ T-cells and CD4+ T-cells as well as other immune cell markers and checkpoints in baseline FFPE blocks of cancer tissue and in optional biopsy and blood specimens.

Although less advanced in clinical development and practice, characterization of ex vivo surface markers on tumor cells, T-cells and other immune cells via multiparametric analysis (e.g. via flow cytometry or mass cytometry) has significant potential to reveal predictive biomarkers given the ability to measure multifarious combinations and to identify combinatorial patterns of expression among diverse cell populations. Using multiparametric assays developed in conjunction with the Dana-Farber Cancer Institute Center for Immunooncology, we will determine evaluate the relative frequencies of T-cell subsets and evaluate the expression of immune checkpoints and other immunologically relevant molecules as noted in Section 9.

Genomic predictive correlates for response to checkpoint blockade have taken several forms. First, and serving as a critical line of evidence supporting this trial, numerous studies have suggested a correlation between mutational and neoepitope burden and response to checkpoint blockade (Le et al., 2015; Rizvi et al., 2015; Snyder et al., 2014). Furthermore, as noted above, identification of microsatellite instability resulting from defects in the mismatch repair pathway and specifically within MLH1, MSH2, MSH6 and PMS2 have been suggested to portend a significantly improved response to checkpoint blockade (Le *et al.*, 2015). As such, we will plan to pursue genomic characterization of tumor and blood samples as noted in Section 9.

At Dana-Farber Cancer Institute, in the Department of Pathology Center for Advanced Molecular Diagnostic at Brigham and Women's Hospital, we have developed a cancer genomic assay to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples "(Wagle et al. High-throughput detection of actionable genomic alterations in clinical tumor samples by targeted, massively parallel sequencing. Cancer Discovery 2012.)" The Oncopanel assay surveys exonic DNA sequences of various cancer genes and multiple regions across genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. The Oncopanel assay assesses genes including mutations and copy number variations in TP53, CCNE1, MYC, ATR, ATM, PTEN and HR pathway and NER pathway genes. This assay will be performed in archival FFPE specimens if it has not already been performed (it is now standard for patients at Dana-Farber Cancer Institute). In cases where Oncopanel sequencing has already been performed on patient samples through DF/HCC protocol 11-104, we will plan to access these results to conserve primary patient samples for additional analyses.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

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

Inclusion criteria applicable to all participants:

3.1.1 Participants must be classified into one of the following cohorts of recurrent or persistent endometrial cancer of any histology:

- **The MSI/*POLE* cohort includes endometrial cancers that are:**
  MSI-H as determined by immunohistochemical complete loss of expression (absence of nuclear immunoreactivity) of at least one of the mismatch repair genes MSH2, MSH6, MLH1 and PMS2. This test is now done routinely for every newly diagnosed endometrial cancer patient in most centers in the US.

AND/OR:

POLE*-mutated**, i.e. endometrial cancers known to harbor mutations in the exonuclease domain (amino acid residues 268–471) of polymerase e (POLE***) as determined by targeted sequencing or other next generation sequencing assay. Any Clinical Laboratory Improvement Amendments (CLIA)-approved genomic test documenting mutations in the exonuclease domain of POLE gene (amino acid residues 268–471) in the tumor will be accepted as proof of presence of POLE mutations and will lead to classification into this patient cohort.

- **The MSS cohorts include:**
  Endometrial cancers that are **MSS** as determined by normal immunohistochemical nuclear expression of all the mismatch repair genes MSH2, MSH6, MLH1 and PMS2. Tumors which have not been sequenced for POLE mutations (i.e. their POLE mutations status is unknown) but are MSS, will be included in this cohort.

3.1.2 All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be >= 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or >= 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI.

3.1.3 Prior Therapy:
There is no upper limit of prior therapies but patients must have had one prior chemotherapeutic regimen for management of endometrial carcinoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy. Any platinum based chemotherapy (single agent platinum or any platinum doublet) administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen. Furthermore,

patients who have only received chemotherapy in the adjuvant setting will be eligible for the study.

- Prior hormonal therapy is allowed (no washout period is required after hormonal therapy).
- Patients must NOT have received any class of drugs targeted to the PD-1/PD-L1 pathway.
- Patients must NOT have received any prior PARP inhibitor therapy (for patients being considered for the avelumab/talazoparib cohort only).
- Patients must NOT have received prior axitinib (for patients being considered for the avelumab/axitinib cohort only)

3.1.4 Age of 18 or greater years. Because insufficient dosing or adverse event data are available on the use of Avelumab, talazoparib, and/or axitinib in participants < 18 years of age, children are excluded from the study. Endometrial cancer is very rare in the pediatric population.

3.1.5 ECOG performance status 0 or 1 (reference Appendix A for ECOG performance status criteria).

3.1.6 Availability of a formalin fixed paraffin embedded (FFPE) block of cancer tissue **OR** 15 unstained 5-micron slides from the original surgery or biopsy or from a biopsy of recurrent disease.

3.1.7 Participants must have normal organ and marrow function as defined below:

absolute neutrophil count	>1,500/mcL
platelets	>100,000/mcL
hemoglobin	≥ 9g/dL
total bilirubin	within normal institutional limits
AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
Creatinine	≤ institutional upper limit of normal

OR

creatinine clearance ≥ 30 mL/min/1.73 m^2 *for participants with creatinine levels above institutional normal*.

CL_{CR} should be estimated according to the Cockcroft-Gault formula as: $CL_{CR}=\{[(140–age) \times weight)]/(72 \times S_{CR})\} \times 0.85$ where CL_{CR} (creatinine clearance) is measured in mL/min, age is expressed in years, weight in kilograms (kg), and S_{CR} (serum creatinine) in mg/dL.

NOTE: Patients with moderate renal impairment (defined as an estimated creatinine clearance of 30-59 mL/min) will receive a reduced starting dose of Talazoparib at 0.75 mg PO QD.

3.1.8 Participant must not be pregnant or breastfeeding given that avelumab is an agent with unknown effects in pregnancy and breastfeeding and the potential for teratogenesis. Females

of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as ≥ 12 months with no menses without an alternative medical cause). Serum pregnancy test (for females of childbearing potential) negative at screening.

3.1.9 The effects of avelumab on the developing human fetus are unknown. For this reason and because some immunomodulatory agents are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 30 days after last avelumab treatment administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.10 Toxicities of prior therapy (excepting alopecia and sensory neuropathy) should be resolved to < grade 2 per the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. All appropriate treatment areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP website at: http://ctep.cancer.gov.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

Additional inclusion criteria for the avelumab/axitinib cohort:

3.1.12 Participants must have adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as systolic BP that must be ≤140 mmHg and diastolic BP that must be ≤90 mmHg on two separate BP readings taken at least 1 hour apart at screening.

3.1.13 Participants must have LVEF ≥ lower limit of normal (LLN) as assessed by either multigated acquisition (MUGA) scan or echocardiogram (ECHO).

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

Exclusion criteria applicable to all participants:

3.2.1 Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Participants who are receiving any other investigational agents.

3.2.3 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to avelumab or any component in its formulations, or compounds of similar chemical or biologic composition to avelumab. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)

3.2.5 Participants with a history of treatment with an anti-PD-1, anti-PD-L1, anti-CTLA-4 or other investigational agents that target immune checkpoint inhibitors.

3.2.6 Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness, which may compromise the efficacy of immunostimulatory therapy.

3.2.7 Positive test for HBV surface antigen.

3.2.8 Positive Hepatitis C antibody and positive confirmatory HCV RNA test. The confirmatory HCV RNA test is not required if the HCV antibody is negative. If Hepatitis C antibody is positive, the confirmatory HCV RNA test should be done and if it is negative, then participants are eligible.

3.2.9 Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day.

3.2.10 Active infection requiring systemic therapy.

3.2.11 Current or prior use of immunosuppressive medication within 7 days prior to enrollment with the following exceptions to this exclusion criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection);
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent;
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

3.2.12 Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

3.2.13 Prior organ transplantation including allogeneic stem-cell transplantation.

3.2.14 Severe gastrointestinal conditions such as clinical or radiological evidence of bowel obstruction within 4 weeks prior to study entry, uncontrolled diarrhea in the last 4 weeks prior to enrollment, or history of inflammatory bowel disease.

3.2.15 Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.16 Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

3.2.17 Known alcohol or drug abuse.

3.2.18 Individuals with a history of a different malignancy are ineligible except for the following circumstances: Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years or if they are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: breast cancer in situ, cervical cancer in situ, and basal cell or squamous cell carcinoma of the skin.

3.2.19 All other significant diseases (for example, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment.

3.2.20 Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

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

3.2.22 Patients may not use natural herbal products or other "folk remedies" while participating in this study. Herbal medications include, but are not limited to St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Additional exclusion criteria for the avelumab/axitinib cohort:

3.2.23 Participants having >1+ proteinuria on urinalysis **or** UPCR >1 will undergo a 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein >1 g/24-hours will be ineligible.

3.2.24 Participants with concern for bowel or serosal involvement will be ineligible, due to the risk of perforation or fistulization with anti-angiogenic agents.

3.2.25 Participants will be ineligible if they have active gastrointestinal bleeding, as evidenced by clinically significant hematemesis, hematochezia, or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy.

3.2.26 Participants will be ineligible if using anticoagulant therapy with oral vitamin K antagonists, novel oral anticoagulants (NOACs), or direct oral anticoagulants (DOACs), inclusive of direct thrombin inhibitors and direct factor Xa inhibitors. Therapeutic use of low molecular weight heparin is allowed. Low dose heparin required for maintenance of patency of central venous access devices are allowed.

3.2.27 Grade ≥3 hemorrhage within 4 weeks preceding Cycle 1 Day 1 treatment.

3.2.28 Ongoing cardiac dysrhythmias of CTCAE Grade≥2, or prolongation of the QTc interval to >500 msec.

3.2.29 Current use or anticipated need for treatment with drugs or foods that are known to be either:

- Strong CYP3A4/5 inhibitors, including administration within 10 days prior to Cycle 1 Day 1 treatment, including but not limited to grapefruit juice, grapefruit-related fruits (Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, conivaptan. The topical use of these medications is allowed if systemic absorption is considered minimal.
- Strong CYP3A4/5 inducers, including administration within 10 days prior to Cycle 1 Day 1 treatment, including but not limited to phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, clevidipine, St. John's wort.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. This disease does not affect men.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible. Participants who do not begin protocol therapy for reasons including ineligibility, inevaluability, and participant drop out will be replaced.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed. Please note that **all sites** must submit the eligibility documents required in section 4.4 and that eligibility must be confirmed by the coordinating center **prior** to participant registration.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Gynecologic Oncology Disease Center by the Project Manager. All sites should contact the Project Manager Madeline Polak at Madeline_Polak@dfci.harvard.edu or 617-632-3743 when they have a potential participant to confirm the study status and enrollment availability.

Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for All Sites

To register a participant, the following documents should be collected by the research nurse or data manager and faxed (617-582-7921) or e-mailed (Madeline_Polak@dfci.harvard.edu) to Madeline Polak, the Project Manager:

- Copy of required laboratory tests: complete blood count with differential, liver functional tests, chemistries
- Copy of the screening visit clinic note, including medical history.
- Copy of the pathology report
- Copy of CT or MRI report
- Documentation for consent process
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist
- Confirmation that sufficient archival tissue is available

The FFPE block or 15 unstained slides should be mailed to the study coordinator at DFCI. Send FFPE block via overnight post to the following address:

Patrice Basada
Dana-Farber Cancer Institute
450 Brookline Ave, DA-122
Boston, MA 02215
Email contact: Patrice_Basada@DFCI.harvard.edu

To complete the registration process, the Project Manager will:

- Follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101) and register the participant on the protocol
- Fax or email the research nurse or data manager at the participating site with the participant study number, and to confirm registration. **Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.**

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager.

5. TREATMENT PLAN

5.1 Treatment Regimens

All treatment will be administered on an outpatient basis.

Applicable to all cohorts: Avelumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons. Avelumab will be administered as a 1-hour IV infusion. In order to mitigate infusion-related reactions, a premedication with an

antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate. Sites should make every effort to target avelumab infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (i.e., infusion time is 50-80 minutes). The exact duration of infusion should be recorded in source documents.

In the MSI/POLE cohort: Avelumab will be administered at 10 mg/kg intravenously on Day 1 and Day 15 of each 4-week cycle (one cycle = 28 days including two infusions) after all procedures/assessments have been completed.

In the MSS cohort receiving avelumab alone: Avelumab will be administered at 10 mg/kg intravenously on Day 1 and Day 15 of each 4-week cycle (one cycle = 28 days including two infusions) after all procedures/assessments have been completed.

In the MSS cohort receiving avelumab + talazoparib: Avelumab will be administered at 10 mg/kg intravenously on Day 1 and Day 15 of each 4-week cycle (one cycle = 28 days, including two infusions) in combination with 1mg PO QD of talazoparib.

In the MSS cohort receiving avelumab + axitinib: Avelumab will be administered as 800mg intravenously on Day 1 and Day 15 of each 28-day cycle (one cycle = 28 days, including two infusions), and axitinib will be administered 5mg twice daily orally.

Reported adverse events and potential risks are described in Sections 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

5.2.1 Pre-Treatment Criteria for Avelumab and Avelumab/Talazoparib Cohorts

Cycle 1, Day 1 (or within 7 days prior to Cycle 1, Day 1)

- Absolute neutrophil count > 1,500/mcL
- Platelets > 100,000/mcL
- Hemoglobin ≥ 9g/dL
- Total bilirubin within normal institutional limits
- AST (SGOT) / ALT (SGPT) ≤ 2.5 × institutional upper limit of normal
- Creatinine ≤ institutional upper limit of normal or creatinine clearance ≥ 30mL/min/1.73 m2 for subjects with creatinine levels above institutional normal
- All toxicities of previous therapy (aside from alopecia and sensory neuropathy) must have resolved to ≤ grade 1
- ECOG performance status of 1 or less
- No evidence of life-threatening medical problems

Subsequent Visits (Days 1 and 15)*

- Absolute neutrophil count > 1,000/mcL
- Platelets ≥ 50,000/mcL
- AST (SGOT)/ALT (SGPT) ≤ 2.5 × institutional upper limit of normal
- Creatinine ≤ institutional upper limit of normal or creatinine clearance ≥ 30 mL/min/1.73 m2 for subjects with creatinine levels above institutional normal
- All toxicities of previous cycles must have resolved to ≤ grade 2
- ECOG performance status of 2 or less.
- No evidence of life-threatening medical problems

For patients who do not achieve hematological recovery on scheduled day of avelumab treatment, complete blood counts should be performed twice weekly until the above defined limits are achieved.

*If the criteria are not met, see **Section 6** for applicable dose modifications and holding. *Please note that dose holds are based on which drug the toxicity is attributed to and study drugs may be held independently of each other, this includes hematologic toxicities.* If applicable based on Section 6, patients who do not meet treatment criteria may be treated with the non-offending agent.

5.2.2 Pre-Treatment Criteria for Avelumab/Axitinib Cohort

Cycle 1 Day 1 (or within preceding 7 days)
Patients must meet eligibility parameters, as detailed in Section 3.

Subsequent Visits (Days 1 & 15)*

- Absolute neutrophil count ≥ 500 /mcL
- Platelets ≥ 25,000/mcL
- Urine protein 0 or 1+ (by urine dipstick)
- Blood pressure ≤150/100
- All toxicities of previous cycles must have resolved to ≤ grade 2
- ECOG performance status of 2 or less
- No evidence of life-threatening medical problems

*If the criteria are not met, see **Section 6** for applicable dose modifications and holding. *Please note that dose holds are based on which drug the toxicity is attributed to and study drugs may be held independently of each other, this includes hematologic toxicities.* If applicable based on Section 6, patients who do not meet treatment criteria may be treated with the non-offending agent.

5.3 Administration

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic and investigational agents. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.1 **Avelumab**

Avelumab Administration & Premedications

Avelumab will be administered at 10 mg/kg on Day 1 and Day 15 of each 4-week cycle for participants in the MSI/POLE cohort, the MSS cohort receiving single agent Avelumab, and the MSS cohort receiving Avelumab in combination with Talazoparib. Avelumab will be administered as 800mg intravenously on Day 1 and Day 15 of each 4-week cycle for participants in the MSS cohort receiving Avelumab in combination with Axitinib. Avelumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

Avelumab will be administered as a 1-hour IV infusion. In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate. Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions

Sites should make every effort to target avelumab infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (i.e., infusion time is 50-80 minutes). The exact duration of infusion should be recorded in source documents. Possible modifications of the infusion rate for the management of infusion-related reactions are described in later sections.

Management of Avelumab-related Infusion Reactions

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions. Patients should be instructed to report any delayed reactions to the Investigator immediately. Avelumab infusion-related reactions should be treated according to the table below.

Prophylactic steroids are NOT permitted.

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

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	• Temporarily discontinue avelumab infusion • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae • Grade 4: Life-threatening consequences; urgent intervention indicated	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment

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

If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment..

If an infusion-related reaction has occurred previously, then for subsequent infusions the following additional pre-medications can be considered: ibuprofen 800mg PO x1, Zyrtec 10mg PO x1, and famotidine 20mg IVx1, all administered 30-60 minutes prior to subsequent avelumab infusions. Furthermore, 250-500 ccs of normal saline IV continuous infusion while avelumab infusion can be considered.

Additionally, if a previous infusion-related reaction occurred, patients must be observed for 4 hours post-infusion in the subsequent avelumab infusion; this observation period can be incrementally decreased by 1 hour in each subsequent infusion (i.e. 3 hours and then 2 hours) until the minimum observation period of 30 minutes post-infusion is reached. The observation period of 30 minutes post-infusion can be omitted for patients who have received 12 or more cycles.

Management of Avelumab Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the ICU should be alerted for possible transfer if required.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, 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 (for example, paracetamol) may be given to patients at the discretion of the investigator.

5.3.2 **Talazoparib**

Talazoparib Administration

Talazoparib will be taken QD at 1 mg PO starting on Cycle 1 Day 1 (C1D1) and treatment should continue until EOT. Patients with moderate renal impairment (defined as an estimated creatinine clearance of 30-59 mL/min) will receive a reduced starting dose of Talazoparib at 0.75 mg PO QD. This dose is based on the recommended phase 2 dose (RP2D) based on the Phase 1 trial of avelumab/talazoparib in advanced tumors. The combination of avelumab and talazoparib was evaluated in a Phase 1 clinical trial in patients with locally advanced or metastatic solid tumors. This study was open in our institution (DFHCC protocol 17-687) and established that the recommended phase 2 dose of talazoparib in combination with avelumab is 1 mg PO QD.

For patients with moderate renal impairment (defined as an estimated creatinine clearance of 30-59 mL/min) a reduced starting dose of Talazoparib at 0.75 mg PO QD is recommended as per the talazoparib IB (Investigator's Brochure of talazoparib (MDV3800, BMN673).On Days 1 and 15 of each cycle, when the patient returns to the clinic for avelumab administration, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and before the avelumab infusion.

Patients should self-administer talazoparib orally QD, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them prior to swallowing.

Patients should be instructed to take talazoparib at approximately the same time each day and to not take more than the prescribed dose at any time.

If a patient misses a day of treatment or vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed. A missed dose for Talazoparib is defined as >12 hours after the scheduled dosing time. Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every cycle.

5.3.3 **Axitinib**

Axitinib Administration

Axitinib will be taken orally twice daily starting on Cycle 1 Day 1 (C1D1). Doses should be taken approximately 12 hours apart and at approximately the same times each day. Axitinib tablets should be swallowed whole with a glass of water. Tablets must not be crushed, split, dissolved, or chewed. Axitinib can be taken with or without food.

Patients must be instructed that if they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken late, up to 3 hours before the next scheduled dose of that day, otherwise, it should be skipped and dosing resumed with subsequent doses as prescribed.

Patients should complete the Dosing Diary and record all doses (including missed, vomited, or extra doses). If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every cycle.

Effect of Antacids

No change in axitinib dosing is recommended in the presence of antacids. The commercial formulation of axitinib utilizes crystal polymorph Form XLI of axitinib, which was determined to have similar plasma exposure (AUC) in either the presence or absence of antacids.

Effect of Food/Meals

A definitive food effect study (A4061053) was conducted in healthy volunteers, showing no clinically significant change in axitinib plasma exposure (AUC) or Cmax in the presence of food. Axitinib can be taken with or without food.

Blood Pressure Monitoring with Axitinib

Patients will be instructed to obtain blood pressure cuffs for home monitoring and instructed to measure their BP at least once daily before taking the morning dose of axitinib. All BP measurements will be recorded in a diary and brought to the nurse or study coordinator at each clinic visit.

Patients should be instructed to contact the site immediately for guidance if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated blood pressure (e.g., headache, visual disturbances), although a different blood pressure threshold for contacting the site may be used according to the investigator's clinical judgment. See **Section 6.1.4** for management of axitinib-related hypertension.

5.3.4 Avelumab & Talazoparib Combination Therapy Administration

On Days 1 and 15 of each cycle, when both avelumab and talazoparib are administered at the investigative site, the following must occur in the order specified:

- All required tests and assessments will be performed, as per the Schedule of Activities and blood will be drawn for PK and ADA assessments (when scheduled);
- Avelumab premedication, as described in Section 5.3.1, and talazoparib will be administered to the patient in any order chosen by the qualified site personnel;
- Avelumab infusion will start within 30-60 minutes after the avelumab premedication was administered and after dosing with talazoparib;
- Blood will be drawn for PK assessments (when scheduled) immediately at the end of the avelumab infusion and the patient will remain in the clinic for observation for at least 30 minutes after the avelumab infusion.

Treatment with avelumab and talazoparib will continue until disease progression is confirmed by the Investigator (except where treatment is allowed beyond progression, as per Section 5.3.6), patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first.

5.3.5 **Avelumab & Axtinib Combination Therapy Administration**

On Days 1 and 15 of each cycle, when both avelumab and axitinib are administered at the investigative site, the following must occur in the order specified:

- All required tests and assessments will be performed, as per the Schedule of Activities
- Avelumab premedication, as described in Section 5.3.1, and axitinib will be administered to the patient in any order chosen by the qualified site personnel
- Avelumab infusion will start within 30-60 minutes after the avelumab premedication was administered, and after dosing with axitinib

Treatment with avelumab and axitinib will continue until disease progression is confirmed by the Investigator (except where treatment is allowed beyond progression, as per Section 5.6), patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first.

5.3.6 **Investigational Product Storage**

The Investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. Any storage conditions stated in the SRSD, which is the IB, will be superseded by the storage conditions stated on the product labels. Reference Investigational Product Manual for storage and administration instructions.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Receipt of materials, door opening and closing, and other routine handling operations where the investigational products are briefly out of the temperature range described in the labeling are not considered excursions.

Specific details regarding information the site should report for each excursion will be provided to the site in the Investigational Product Manual.

5.4 Concomitant Medication and Supportive Care Guidelines

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 30 days after the last dose of study treatment. All concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF including supportive care drugs (e.g., antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g., transfusions).

Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.4.1 Concomitant Surgery

In case of surgical procedure trial treatment should be delayed. Re-initiation should be discussed with the Overall PI.

5.4.2 Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline; otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

5.4.3 Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 4 weeks (1 cycle) of treatment but they may be used at any time to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. 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 at the discretion of the treating physician.

5.4.4 **Steroid Use**

Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes (Schleimer *et al.*, 1984). 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-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes (Weber et al., 2012). Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 6, Avelumab Management of Immune-related Adverse Events.

- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

- Prophylactic use, e.g., for the prevention of acute infusion-related reactions: is prohibited.

5.4.5 **Prohibited Concomitant Medications and Therapies**

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

- Any anti-cancer systemic chemotherapy or biologic therapy, including vitamins that are used as anti-cancer treatments, other than avelumab, talazoparib and axitinib depending on the cohort

- Immunotherapy not specified in this protocol

- Any investigational agents other than Avelumab or talazoparib and axitinib depending on the cohort

- Any vaccination for the prevention of infectious disease while on avelumab treatment except for the administration of inactivated vaccines.

- Herbal remedies with immunostimulating properties or known to potentially interfere with major organ function

- P-gp inhibitors (amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine,ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil) while on **talazoparib** treatment. The following inhibitors of P-gp may be taken with additional caution, at the Investigator's discretion: P-gp inhibitors (atorvastatin, azithromycin, conivaptan, diltiazem, diosmin, eliglustat, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis tract).

- P-gp inducers (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort) while on **talazoparib** treatment.

- BCRP inhibitors (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag) while on **talazoparib** treatment.

- Strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) while taking **axitinib**.

- Strong CYP3A4/5 inducers (e.g. rifampin, dexamethasone, phenytoin, carbameazepine, rifabutin, rifapentine, phenobarbital, St John's wort) while taking **axitinib**.

- Grapefruit and grapefruit juice should be avoided while taking **axitinib**

There are no prohibited therapies during the Post-Treatment Follow-up Phase. If there is a clinical indication for one of the medications or vaccines specifically prohibited during the trial, discontinuation from study treatment may be required. The Investigator should consult with the sponsor about individual cases.

5.5 Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or magnetic resonance imaging (MRI) scans. Brain CT or MRI scan at baseline is only required when there is suspected brain metastases or new lesion during the study. The CT scans should be performed with contrast agents unless contraindicated for medical reasons.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline (screening) of starting therapy and every 8 weeks thereafter. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (e.g., symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 4 weeks). Complete, partial responses and progressive disease must be confirmed on repeated imaging $\geqq$ 4 weeks after initial documentation, but not more than 8 weeks after initial documentation.

Assessment of response will be made using RECIST version 1.1 and as per immune-related RECIST criteria (irRECIST).

5.6 Treatment After Initial Evidence of Radiologic Disease Progression

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

If radiologic imaging shows progression, tumor assessment should be repeated ≥ 6 weeks later in order to rule out pseudo-progression, at the investigator's discretion. Depending on the cohort, Avelumab and/or Talazoparib and/or Axitinib may be continued at the investigator's discretion during this period. If repeat imaging shows CR, PR or SD compared to the first scan that showed disease progression, treatment with avelumab and/or Talazoparib and/or Axitinib may be continued or resumed.

If the repeat imaging demonstrates PD compared to the first scan that showed disease progression, patients should be discontinued from all study treatment. Patients may receive avelumab and/or Talazoparib and/or Axitinib during this period if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease by radiographic imaging as assessed by treating clinician.
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

5.7 Duration of Therapy / Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) as defined in Section 6 or in the judgment of the treating clinician,
- Participant decides to withdraw from the study,
- Pregnancy, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be

documented in the case report form (CRF). Alternative care options will be discussed with the participant.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall Principal Investigator, Panagiotis Konstantinopoulos, MD, at 617-632-3000 (pager) and pkonstantinopoulos@partners.org.

5.8 Duration of Follow Up

Participants will be followed for 3 years by phone after removal from study or until death, whichever occurs first. Survival status should be checked every 6 months during that time. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Date and cause of death should be provided for participants who become deceased within the 3-year interval following removal from the study. Should a participant become pregnant while on trial, the patient will be withdrawn from the study. However, the outcome of the pregnancy and the newborn's health, if the pregnancy is carried to term, will be monitored.

5.9 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Pregnancy

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS, MODIFICATIONS, AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

Every effort should be made to administer study treatment on the planned dose and schedule.

In the event of significant toxicity, dosing may be interrupted, delayed and /or reduced only as described for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

> **Avelumab**: No dose reductions are permitted in this study, but the next infusion may be omitted based on persisting toxicity. If Day 1 Avelumab is held, the dose will be omitted and resumed on Day 15 of the cycle as long as the pre-treatment criteria in section 5.2 are met. The same will apply if Day 15 is held, the dose will be omitted and resumed on Day 1 of the next cycle as long as pre-treatment criteria are met.
>
> **Talazoparib**: Dose modifications (dose interruptions or dose reductions) may be implemented to manage toxicities.
>
> **Axitinib**: Dose modifications (dose interruptions or reductions) may be implemented to manage toxicities.

All dose modifications must be clearly documented in the patient's medical chart and in the CRF. In addition to dose modifications, Investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the event of a treatment interruption for reasons other than treatment-related toxicity (e.g., elective surgery) for >7 consecutive days, treatment resumption will be decided in consultation with the Sponsor.

6.1 Dose Reductions of Talazoparib

Following dosing interruption due to toxicity at any time in the study, the talazoparib dose may need to be reduced, based on the worst toxicity reported, when treatment is resumed. Dose reduction should be made in accordance with the guidance provided in the following table. Dose reduction of talazoparib by 1 dose level at a time will be allowed depending on the starting dose and type and severity of toxicity encountered. Doses less than 0.25 mg are not permitted. Patients unable to tolerate 0.25 mg QD, will be permanently discontinued from the talazoparib, but may continue on single agent avelumab. Available dose levels for dose reductions are listed in the table below.

Dose Levels for Dose Reductions of Talazoparib

Dose Level	Talazoparib Dose (Oral)
D-0	1mg QD
D-1	0.75mg QD
D-2	0.5mg QD
D-3	0.25mg QD[a]

[a] Talazoparib dose de-escalation below 0.25 mg QD is not allowed.

D = dose; QD = once daily

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intra-patient dose re-escalation is not allowed.

If a dose reduction is required, the patient may need to return to the clinic to receive new drug supply prior to the next scheduled visit since dosage strengths of the capsules may be different. Site personnel must ensure the patients are instructed how to take the reduced dose and that the patients have the correct dosage strength for the reduced dose.

6.2 Dose Reductions of Axitinib

The dose of axitinib may need to be reduced due to toxicity, based on the worst toxicity reported, at any time during the study. Dose reduction should be made in accordance with the guidance provided in the table below:

Dose Levels for Dose Reductions of Axitinib

Dose Level	Axitinib Dose (Oral)
D-0	5mg BID
D-1	3mg BID
D-2	2mg BID

BID=twice daily

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intra-patient dose re-escalation is not allowed.

If a dose reduction is required, the patient may need to return to the clinic to receive new drug supply prior to the next scheduled visit since dosage strengths of the tablets may be different. Site personnel must ensure the patients are instructed how to take the reduced dose and that the patients have the correct dosage strength for the reduced dose.

6.3 Study Treatment Modifications for Avelumab & Talazoparib Drug-Related Toxicity

These modifications are excluding infusion-related reactions and immune-related adverse events.

For patients receiving avelumab, either as a single agent or in combination with talazoparib, any AE suspected to be immune-related should be managed according to the guidance for management of irAEs in Section 6.1.6.

Recommended avelumab and talazoparib treatment modifications in case of investigational product related toxicity are shown in Table 6. The specific guidelines are applicable in cases which can be attributed to one of the investigational products. The instructions should be followed in the column regarding the investigational product that toxicity is attributed to. In cases where an AE is possibly related to both investigational products, the guidelines in both columns for both investigational products should be followed. Patients who stop avelumab or talazoparib for unacceptable toxicity may continue treatment with the investigational product that is not considered to be responsible for the toxicity observed. Dose holds can be independent of one another. Hold only the drug that is suspected to be causing the toxicity. Talazoparib may be resumed independently of Avelumab.

The Thyroid function tests do not need to be resulted before treatment begins if the previous cycle's results were within normal limits (WNL).

Thyroid function test results will need to be resulted and reviewed before treatment begins if the previous cycle's results were not WNL and required therapeutic intervention.

Table 6. Talazoparib and Avelumab Treatment Modifications for Drug-Related Toxicity (Excluding Infusion-Related Reactions and Immune-Related AEs)

	Talazoparib	Avelumab
Hematologic Toxicities		
• **Grade 1 and Grade 2**	• No requirement for dose interruption or dose reduction.	• Continue as per schedule.
• **Anemia Grade ≥3** (hemoglobin <8 g/dL)	• Hold talazoparib and monitor weekly until resolves to >9g/dL. • Resume Talazoparib at a reduced dose, per Section 6.1.1 • Permanently discontinue if persists for >4 weeks without recovery to baseline. Refer to hematologist for evaluation including assessment of possible MDS/AML.	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).

• **Neutropenia Grade ≥3** (ANC <1000/μL)	• Hold talazoparib and monitor weekly until resolves to ANC ≥1500/μL. • Resume Talazoparib at a reduced dose, per Section 6.1.1 • Permanently discontinue talazoparib if persists for >4 weeks without recovery to ANC ≥1000/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML.	• Hold avelumab. Re-initiate avelumab once toxicity Grade ≤2 (ANC ≥1000/μL) or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).
• **Thrombocytopenia Grade ≥3** (platelets <50,000/μL)	• Hold talazoparib and monitor weekly until resolves to ≥50,000/μL • Resume talazoparib reduced by 1 dose level, per Section 6.1.1 • Permanently discontinue talazoparib if persists for >4 weeks without recovery to platelets ≥50,000/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML.	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤2 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).
Non-hematologic Toxicities		
Grade 1 and Grade 2	• No requirement for dose interruption or dose reduction. • For suspected immune-related toxicities due to avelumab that require avelumab delay or discontinuation as per Section 6.6, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.	• Continue as per schedule. • For suspected immune-related toxicities due to avelumab follow guidance in Section 6.6.

Grade 3	• Hold talazoparib.
	• Resume talazoparib reduced by 1 dose level, per Section 6.1 if toxicity resolves to Grade ≤1 or baseline within 4 weeks.
	  • **Exceptions are:** Nausea, vomiting, or diarrhea lasting ≤72 hours; fatigue lasting <5 days; hypertension controlled with medical therapy; increase in indirect bilirubin indicative of Gilbert's syndrome; serum lipase or amylase lasting ≤7 consecutive days without clinical signs or symptoms of pancreatitis; endocrinopathies controlled with hormonal therapy; laboratory values that do not have any clinical correlate.
		• Hold avelumab.
		• Resume once toxicity is Grade ≤1 or baseline.
		• Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
		  • **Exceptions are:** Laboratory values that do not have any clinical correlate.
		• For suspected immune-related toxicities follow guidance in Section 6.6.

	• If the same Grade 3 toxicity recurs, reduce by 1 dose level. • Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • Permanently discontinue if Grade 3 liver test abnormality. Rechallenge may be considered once toxicity is Grade ≤1 or baseline, if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is identified. • For suspected immune-related toxicities due to avelumab that require avelumab delay or discontinuation as per Section 6.6, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.	

Grade 4	• Permanently discontinue talazoparib
	  • **Exceptions are:** Laboratory values that do not have any clinical correlate.
	• For suspected immune-related toxicities follow guidance in Section 6.6
		• Permanently discontinue avelumab
		  • **Exceptions are:** Laboratory values that do not have any clinical correlate.
		• For suspected immune-related toxicities follow guidance in Section 6.6

Abbreviation ANC: Absolute Neutrophil Count; MDS=Myelodysplastic Syndrome.

6.4 Study Treatment Modifications for Avelumab & Axitinib

These modifications are excluding infusion-related reactions and immune-related adverse events. For patients receiving avelumab, either as a single agent or in combination with axitinib, any AE suspected to be immune-related should be managed according to the guidance for management of irAEs in Section 6.1.6.

Recommended avelumab and axitinib treatment modifications in case of investigational product related toxicity are shown in the following table. The specific guidelines are applicable in cases which can be attributed to one of the investigational products. The instructions should be followed in the column regarding the investigational product that toxicity is attributed to. In cases where an AE is possibly related to both investigational products, the guidelines in both columns for both investigational products should be followed. Patients who stop avelumab or axitinib for unacceptable toxicity may continue treatment with the investigational product that is not considered to be responsible for the toxicity observed. Dose holds can be independent of one another. Hold only the drug that is suspected to be causing the toxicity. Axitinib may be resumed independently of avelumab.

The Thyroid function tests do not need to be resulted before treatment begins if the previous cycle's results were within normal limits (WNL). Thyroid function test results will need to be resulted and reviewed before treatment begins if the previous cycle's results were not WNL and required therapeutic intervention.

Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
Hematologic Abnormalities	Grade 1	• Continue at the same dose level.	• Continue as per schedule.
	Grade 2	• Continue at the same dose level.	• Continue as per schedule.
	Grade 3	• Continue at the same dose level.	• Withhold avelumab. • Re-initiate avelumab once toxicity is Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks (consider consult with the medical monitor before permanently discontinuing the treatment). **Exceptions are**: Laboratory values that do not have any clinical correlate.
	Grade 4	• Withhold until recovery to Grade ≤2. • Then, reduce by 1 dose level and resume treatment. • For Grade 4 lymphopenia not associated with clinical events (e.g., opportunistic infection) axitinib treatment may continue without interruption.	• Permanently discontinue avelumab (consider consult with medical monitor before permanently discontinuing the treatment). **Exceptions are:** Laboratory values that do not have any clinical correlate.
Proteinuria	Dipstick negative or shows 1+ (Grade 1)	• Continue at the same dose level.	• Continue as per schedule.
	If dipstick shows >1+, perform 24 hour urine collection. Dosing may continue while waiting for test results		
	<2 g proteinuria/ 24 hour	• Continue at the same dose level.	

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
	≥2 g proteinuria/ 24 hours	• Withhold until proteinuria is <2 g/24 hours. • Repeat 24-hour urine collection for proteinuria and creatinine clearance (interval at investigator discretion) until proteinuria is <2 g/24 hours. • Then, resume at the same dose level or reduce by 1 dose level as per investigator judgment.	
Hypertension	2 systolic BP readings separated by at least 1 hour show systolic pressure ≤150 mm Hg (one or both readings) And 2 diastolic BP readings separated by at least 1 hour show diastolic pressure ≤100 mm Hg (one or both readings)	• Continue at the same dose level. • See below for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.
	2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	• If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and continue at the same dose level. • If on maximal antihypertensive treatment, reduce by 1 dose level. • See below for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
	2 systolic BP readings separated by at least 1 hour show systolic pressure >160 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	• Withhold until BP is less than 150/100 mm Hg[1] and adjust antihypertensive medication. • Then, reduce by 1 dose level and resume treatment. [1] If axitinib dosing is temporarily discontinued, patients receiving antihypertensive medications should monitor closely for hypotension. The plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dosing interruption. • See below for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.
	Recurrent hypertension following previous dose reduction (2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg) OR Recurrent diastolic BP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	• Repeat dose reduction by one lower dose level. • See below for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
Infusion-related Reaction	Grade 1-4	• Continue at the same dose level.	• See Section 5.3.1
Hypersensitivity reactions	Grade 3-4	• Continue at the same dose level.	• See Section 5.3.1
Tumor lysis syndrome	Grade 1-4	• See Other Non-Hematologic Toxicities and/or Laboratory Abnormalities.	• Treat TLS as per standard of care institutional guidelines
Immune-related AE (irAE)	Grade 1-4	• Grade 1: continue at the same dose level. • Grade 2-4: hold treatment until recovery to Grade ≤1 and restart axitinib at the same dose level for Grade 2 and at reduced dose level for Grade 3-4.	• See Section 6.6
Stevens-Johnson syndrome	Grade 3-4	• Permanent discontinuation	• Permanent discontinuation
Other Non-hematologic Toxicities and Laboratory Abnormalities	Grade 1	• Continue at the same dose level.	• Continue as per schedule
	Grade 2	• Continue at the same dose level.	• Continue as per schedule

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
Other Non-hematologic Toxicities and Laboratory Abnormalities (continued)	Grade 3	• Reduce by 1 dose level. • Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry laboratory abnormalities: continue at the same dose or reduce by 1 dose level as per investigator judgment.	• Withhold avelumab. • Re-initiate avelumab once toxicity is Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline value within 12 weeks (consider consult with medical monitor before permanently discontinuing the treatment). **Exceptions are**: • Laboratory values that do not have any clinical correlate (e.g., amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis). • Nausea and vomiting controlled by medical therapy. • Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
Other Non-hematologic Toxicities and Laboratory Abnormalities (continued)	Grade 4	• Hold treatment until recovery to Grade ≤2. • Then, reduce by 1 dose level and resume treatment. • Grade 4 asymptomatic biochemistry laboratory abnormality: study treatment may continue without interruption.	• Permanently discontinue avelumab (consider consult with the medical monitor before permanently discontinuing the treatment). **Exceptions are:** • Laboratory values that do not have any clinical correlate.

Decline in LVEF

In case of LVEF decline in patients treated with the axitinib plus avelumab combination, Investigators are encouraged to consult with the Sponsor to discuss the management of axitinib therapy independently of any actions implemented for avelumab and the Investigator's causality assessment of the event.

Management of Axitinib-Related Hypertension

To treat an increase in BP, standard antihypertensives may be used (for example, thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, and dihydropyridine (DHP) calcium channel blockers), although bradycardic agents (such as beta-adrenergic blockers with or without alpha-blocking properties, and non-DHP calcium channel blockers, clonidine, digoxin) should be avoided to the extent possible.

6.5 Treatment Modifications for Infusion-Related Reactions Associated with Avelumab

Recommended treatment modifications in case of avelumab infusion-related reactions are shown in the following table.

Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI CTCAE Severity Grade	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 (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume avelumab infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.[a]
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject. • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

a. If avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.

Abbreviations: NCI-CTCAE=National Cancer Institute-Common for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous.

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated above (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed. At the next dose, the Investigator may consider the addition of H2 blocker antihistamines (e.g., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic corticosteroids are not permitted.

6.6 Immune-related Adverse Events/Toxicity Management

For patients receiving avelumab, any AE suspected to be immune-related (i.e. an irAE) should be managed according to the guidance for management of irAEs per the table below.

Treatment of irAEs is mainly dependent on severity (NCI CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent): manage similar to Grades 3 to 4 AE.
- Grades 3 to 4: treat with high dose corticosteroids; if suspected to be related to avelumab, talazoparib should be withhold until toxicity resolves to Grade □1 or baseline.

For Grade ≥3 immune-related toxicities suspected to be related to avelumab, talazoparib should be withheld until toxicity resolves to Grade ≤1 or baseline.

Specific management of irAEs should proceed as described in the table below.

Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/ Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline; Colitis: asymptomatic	Continue avelumab therapy, Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately. If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy. If persists > 5-7 days or

ADL Colitis: abdominal pain; blood in stool		recurs: Treat as Grade 3 or 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone 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 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis
Dermatologic irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue Avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists >1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or 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 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

	Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
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 prednisone or 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 following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: 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. Hospitalize. Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab,

	antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤ 1: Resume routine monitoring, resume avelumab therapy If elevation persists > 5-7 days or worsens: Treat as Grade 3 to 4
Grade 3 to 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 prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	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 If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**

Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and	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

	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.	myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
*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		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

	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)	
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	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).

	inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids	In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed	If improves to Grade ≤ 1: Taper steroids over at least 1 month

	Add prophylactic antibiotics for opportunistic infections Specialty consult.	
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.

7. ADVERSE EVENT: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for Avelumab (MSB0010718C)

Frequent toxicities (between a 10-50% chance that this will happen): Tiredness, and reactions (including allergic reactions) that occur during or following infusion (may include chills, fever, muscle pain, shortness of breath, low or high blood pressure).

Occasional toxicities (between a 1-10% chance that this will happen): Nausea, diarrhea, which is frequent, loose watery stools, which can cause dehydration and may require hospitalization and treatment with intravenous fluids. Severe and prolonged diarrhea can be life-threatening. Chills, reduced appetite, joint pain, underactive thyroid gland (possible weight gain, heart failure, and/or constipation), itchy skin, vomiting, flu-like symptoms including aches, fever and chills, and skin rash. Low number of red blood cells that can causes tiredness and shortness of breath, and may require a blood transfusion. Abnormally high levels of enzymes produced by the liver meaning that the liver is not functioning properly and can cause fatigue, and jaundice (yellowing of the

skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening. Muscle pain, weakness, headache, and constipation.

Reactions (including allergic reactions) that occur during or following the infusion (may include chills, fever, muscle pain, shortness of breath, and decrease or increase in blood pressure) are mostly mild or moderate and should resolve with a slowdown or discontinuation of the infusion and administration of medications to control the symptoms such as anti-allergic and pain-killer drugs. In some cases these reactions may be severe (less than 1% of patients) and could require intensive medical support and even life threatening reactions may occur.

Side effects resulting from an increased activity of the immune system have also been observed. Most of these side effects are reversible, which means they will stop once treatment with avelumab is discontinued, however in some cases these reactions may be severe (approximately 2% of patients) and could lead to death in rare cases. The reactions that are more severe may require treatment with drugs that decrease the immune system function, also called immunosuppressant drugs (like corticosteroids or more potent drugs, such as infliximab).

The side effects resulting from an increased activity of the immune system that were observed in patients receiving avelumab include the following:

- Immune side effects observed in 5%-10% of participants: inflammation of the skin (could include skin rash, itchy skin, redness or blisters in the skin).
- Immune side effects observed in 1%-5% of participants: abnormal function of the thyroid gland. Low thyroid function may cause fatigue, weight gain, fluid retention, sensitivity to cold & mental apathy. Can be serious or life threatening. High thyroid function may cause weight loss, rapid heartbeat, sweating, trouble with heat, nervousness. May require medical intervention to resolve symptoms. Inflammation of the thyroid could cause possible tenderness in the neck. Inflammation of the lungs (this could cause cough, difficulty breathing and require hospitalization). Immune side effects observed in less than1% of participants: inflammation of the large intestine which may cause stomach pain with loose or watery stools. Inflammation of the liver which may cause you to feel not hungry, tired, have a mild fever, muscle or joint aches, nausea and vomiting and stomach pain. Low function of the adrenal glands causing fatigue, loss of appetite, depression, weight loss and low blood pressure. Inflammation of the eyes causing blurred vision, light sensitivity and/or redness. Inflammation of the muscles causing cramping and muscle pain. Inflammation of the heart may cause chest pain, or heart failure.

7.1.2 **Adverse Events for Axitinib**

The safety of axitinib has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described reflect exposure to axitinib in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib.

The most common (≥20%) adverse reactions observed following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

Selected adverse reactions (all grades) that were reported in <10% of patients treated with axitinib included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), lipase increased (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), transient ischemic attack (1%), and RPLS (<1%).

Hypertension & Hypertensive Crisis
In a controlled clinical study with axitinib for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving axitinib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving axitinib; hypertensive crisis was reported in 2/359 patients (<1%) receiving axitinib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axtinib. Hypertension was managed with standard antihypertensive therapy. Discontinuation of axitinib treatment due to hypertension occurred in 1/359 patients (<1%) receiving axitinib.

Arterial Thromboembolic Events
In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with axitinib for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving axitinib, and fatal cerebrovascular accident was reported in 1/359 patients receiving axitinib. In clinical trials with axitinib, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 17/715 patients (2%), with two deaths secondary to cerebrovascular accident.

Venous Thromboembolic Events
In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with axitinib for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving axitinib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving axitinib (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and retinal vein thrombosis). Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving axitinib. In clinical trials with axitinib, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to pulmonary embolism.

Hemorrhage
In a controlled clinical study with axitinib for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving axitinib. Grade 3/4 hemorrhagic events

were reported in 5/359 (1%) patients receiving axitinib (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena). Fatal hemorrhage was reported in 1/359 patients (<1%) receiving axitinib (gastric hemorrhage).

Gastrointestinal Perforation and Fistula Formation
In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving axitinib. In clinical trials with axitinib, gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).

Thyroid Dysfunction
In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving axitinib. Hyperthyroidism was reported in 4/359 patients (1%) receiving axitinib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving axitinib.

Reversible Posterior Leukoencephalopathy Syndrome
In a controlled clinical study with axitinib for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving axitinib. There were two additional reports of RPLS in other clinical trials with axitinib. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS.

Proteinuria
In a controlled clinical study with axitinib for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving axitinib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving axitinib.

Elevation of Liver Enzymes
In a controlled clinical study with axitinib for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the axitinib arm and 2% of patients on the sorafenib arm.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution of the AE:**
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

7.3 Expedited Adverse Event Reporting to Overall PI

7.3.1 Investigators must report **within 1 business day of investigator awareness** to the Overall PI any serious adverse event (SAE) that occurs **from the time that the subject provides informed consent**, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 calendar days after the last administration of the study treatment.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated	Not required	Not required	5 calendar	5 calendar	24 hours*

Unlikely			days[#]	days	
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Expedited Reporting to Pfizer Inc.

All observed or volunteered AEs regardless of study treatment or suspected causal relationship to the study treatment(s) will be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor-Investigator, any non-serious adverse event that is determined by the Sponsor-Investigator to be serious will be reported by the Sponsor-Investigator as an SAE. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

7.4.1 Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative **begins from the time that the subject provides informed consent**, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 calendar days after the last administration of the study treatment.

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor-investigator if the investigator becomes aware of them; at a minimum, all SAEs that the

investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor-investigator.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of study treatment through 30 calendar days after the last administration of the study treatment.

During the post-treatment safety follow-up (beyond 30 days through 90calendar days after last study treatment administration), AEs serious or non-serious, suspected to be related to the study treatment based on investigator's assessment, should be recorded on the CRF.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

7.4.2 Serious Adverse Event Reporting to Pfizer Inc.

If an SAE occurs, Pfizer is to be notified within 1 business day of Investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding cases and occupational exposure.

Steps for reporting Serious Adverse Events to Pfizer Worldwide Safety:

- All SAEs, whether related or unrelated to avelumab and all pregnancies must be reported to Pfizer (by the investigator or designee) within 24 hours (i.e. 1 business day) using the MedWatch Form FDA 3500A-Mandatory Reporting and the Pfizer Reportable Event Fax Cover Sheet.
- All SAEs should be reported via confirmed facsimile (fax) transmission to:

  Pfizer U.S. Clinical Trial Department SAE Fax Number: 1-866-997-8322.

  OR scanned and reported via electronic mail to:

  SAE Email Address: USA.AEReporting@pfizer.com

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours (i.e. 1 business day) after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to Pfizer in

accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

7.4.3 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE (version 4.03) Grade 5.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

7.4.4 Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values $\geq$ 3times the upper limit of normal

(XULN) concurrent with a total bilirubin values ≥ 2X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2X ULN or not available.

- For patients with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and ≥ 3 times ULN or ≥ 8 times ULN (whichever is smaller).
- Concurrent with
    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN or if the value reaches ≥ 3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombintime (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

7.4.5 Hospitalization

Hospitalization is defined as any initial admission (even less than 24hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance. Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities; Nursing homes;

- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8 DRUG FORMULATION INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.

8.1 Avelumab

8.2.2 Description

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1.

The calculated molecular weight of the molecule is 143,832 Dalton. The antibody is produced by mammalian cell culture in a serum-free growth medium. The antibody is purified by affinity, ion-exchange, and mix-mode chromatography. The process also includes specific viral inactivation and removal steps. The antibody is then transferred into formulation buffer and brought to the desired concentration.

8.2.3 Form

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Each single-use 10 mg/mL vial 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 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 Ph. Eur. and/or the current USP are used.

8.2.4 Storage and Stability

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long-term stability studies with avelumab. Do not freeze. Protect from light. Do not shake vigorously. See the Investigational Product Manual for storage conditions of avelumab once diluted.

Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

For 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. 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.

8.2.5 Preparation and Handling

For administration in this trial, avelumab must be diluted with 0.9% sodium chloride (normal saline solution). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the DAI. Must use tubing with in-line, low protein binding 0.2 micron filter made of polyether sulfone (PES) during administration.

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 dosing for every cycle to ensure they did not experience either a weight loss or gain ≥10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain ≥10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

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

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

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 Investigational Product Supplies

Each site is responsible for requesting the investigational product from Pfizer Inc. using the Drug Supply Request Form. Investigational product supplies will be shipped to the study sites by Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD), and will include a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

8.2.7 Administration

Avelumab will be administered intravenously via a 1-hour infusion every 14 days according to the protocol and dosing schedule described in Section 5.

Sites should make every effort to target avelumab infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (i.e., infusion time is 50-80 minutes). The exact duration of infusion should be recorded in source documents. Possible modifications of the infusion rate for the management of infusion-related reactions are described in later sections.

8.2.8 Accountability

The Investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities.

The prescribed dose must be recorded in the patient's medical records. Drug dispensing must follow institutional policies. Copies must be provided to Pfizer.

At the end of the trial, or at appropriate points during the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented. If drug destruction is not permitted locally, Pfizer should be contacted for further directions.

8.2.9 Destruction and Return

The Sponsor or designee will provide guidance on the destruction of unused investigational product (e.g., at the site). If destruction is authorized to take place at the study site, the

investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

8.2 Talazoparib

8.2.1 Description

Talazoparib is a potent, orally bioavailable small molecule PARP inhibitor.

8.2.10 Form

Talazoparib will be provided as capsules for oral administration. The 0.25 mg (opaque white, size 4) and 1.0 mg (opaque pale-pink, size 4) capsules will be supplied in separate bottles and labeled according to local regulatory requirements. Talazoparib is packaged in induction sealed, high-density polyethylene bottles with child-resistant caps with 30 capsules of a single strength per bottle.

8.2.11 Storage and Stability

Talazoparib is stored at room temperature (15°C–30°C; 59°F–86°F) or per approved local label. Site staff will instruct patients on the proper storage requirements for take home investigational product, as talazoparib will be self-administered at home by patients.

8.2.12 Preparation and Handling

Talazoparib should be dispensed on the Day 1 Visit of every cycle. A qualified staff member will dispense the investigational product in the bottles provided, in quantities of 30 capsules per bottle. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site on the Day 1 Visit of every cycle.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the dispensing, handling, and safe disposal of talazoparib. Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment.40
Patients should be advised that oral anti-cancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

8.2.13 Investigational Product Supplies

Each site is responsible for requesting the investigational product from Pfizer Inc. using the Drug Supply Request Form. Investigational product supplies will be shipped to the study sites by Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD), and will include a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations

8.2.14 Administration

Talazoparib will be taken QD at 0.25mg, 0.5 mg, 0.75 mg, or 1 mg starting on Cycle 1 Day 1 (C1D1) and treatment should continue until EOT. Patients with moderate renal impairment (defined as an estimated creatinine clearance of 30-59 mL/min) will receive a reduced starting dose of Talazoparib at 0.75 mg PO QD. On Days 1 and 15 of each cycle, when the patient returns to the clinic for avelumab administration, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and before the avelumab infusion.

Patients should self-administer talazoparib orally QD, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them prior to swallowing.

Patients should be instructed to take talazoparib at approximately the same time each day and to not take more than the prescribed dose at any time.

If a patient misses a day of treatment or vomits any time after taking a dose, he/she must be instructed not to “make it up” but to resume subsequent doses the next day as prescribed.

Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every cycle.

8.2.15 Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All unused talazoparib must be returned to the Investigator or designated investigative site personnel by each patient on Day 1 of every the trial in order to perform and document drug accountability

8.2.16 Destruction and Return

The Sponsor or designee will provide guidance on the destruction of unused investigational product (e.g., at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

8.3 Axitinib

8.3.1 Description

Axitinib is a potent, orally bioavailable small molecule inhibitor of VEGF receptors 1-3. Axitinib has the chemical name N-methyl-2-[3-((E)2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide.

8.3.2 Form

Axitinib will be supplied as red, film-coated tablets containing either 1 mg or 5 mg of axitinib together with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry® II red 32K15441 as inactive ingredients. The Opadry II red 32K15441 film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide

8.3.3 Storage and Stability

Axitinib tablets are red film-coated, triangular tablets debossed with “Pfizer” on one side and “5 XNB” on the other; available in bottles of 60: NDC 0069-0151-11.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Site staff will instruct patients on the proper storage requirements for take home investigational product, as axitinib will be self-administered at home by patients

8.3.4 Preparation and Handling

Axitinib should be dispensed on the Day 1 visit of every cycle. A qualified staff member will dispense the investigational product in the bottles provided, in quantities of 60 tablets per bottle. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site on the Day 1 visit of every cycle.

8.3.5 Investigational Product Supplies

Each site is responsible for requesting the investigational product from Pfizer Inc. using the Drug

Supply Request Form. Investigational product supplies will be shipped to the study sites by Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD), and will include a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulation

8.3.6 Administration

Axitinib will be taken 5mg twice daily by mouth starting on Cycle 1 Day 1 (C1D1) and treatment should continue until EOT.

On Days 1 and 15 of each cycle, when the patient returns to the clinic for avelumab administration, the daily dose of axitinib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and before the avelumab infusion.

Patients should self-administer axitinib orally BID, with or without food. The tablets should be swallowed whole with a glass of water without chewing, dissolving, or opening them prior to swallowing. Doses should be taken approximately 12 hours apart and at approximately the same times each day.

If the patient vomits or misses a dose, an additional dose should NOT be taken. The next prescribed dose should be taken at the usual time.

Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every cycle.

8.3.7 Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All unused axitinib must be returned to the Investigator or designated investigative site personnel by each patient on Day 1 of every the trial in order to perform and document drug accountability.

8.3.8 Destruction and Return

The Sponsor or designee will provide guidance on the destruction of unused investigational product (e.g., at the site). If destruction is authorized to take place at the study site, the

investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented

9 BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

As noted in Section 2.4, the development of biomarkers for response and for toxicity associated with avelumab and other checkpoint inhibitors represents a substantial priority for the development of immunotherapeutic strategies in oncology. As such, we will request collection and banking of serial samples of blood as well as optional (although encouraged) core biopsies throughout the course of the trial as noted in Section 9.1.

9.1 Sample Collection

9.1.1 Blood Sample Collection for HLA-typing, anti-avelumab antibodies, and Exploratory Biomarker Assessment

Blood biospecimens (30 mL of blood: 20 mL into two purple top [EDTA] tubes (10 mL blood per tube) and 10 mL into one red top tube) will be collected from patients before the start of the first infusion on Cycle1, Day1; Cycle2, Day1; Cycle3, Day1; and at End of Treatment, with the option for further collection while on study protocol. If a sample was collected at screening it does not have to be collected at Day 1 prior to the infusion.

A. Processing for Red-Topped Tube (~10ml for plasma/serum):
- Spin down for 10 min at 2600 RPM, after which the plasma is taken as supernatant.
- Gives rise to 2 cryovials for plasma.
- Each daughter cryovial has ~2ml of plasma.

B. Processing for TWO Purple-Topped Tube (~20ml for whole blood):
- Aliquot ~2mL of whole blood into each cryovial.
- (Gives rise to 8 cryovials for whole blood.)

All tubes will be stored in cryovials in -80°C freezers and batched shipped on dry ice to:

Patrice Basada
Dana-Farber Cancer Institute
450 Brookline Ave, DA-122
Boston, MA 02215
Phone: 617-632-4792
Email: Patrice_Basada @DFCI.harvard.edu

Samples will be used for HLA-typing, to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development

of resistance to avelumab or other immunotherapeutics, or the identification of those patients who might benefit from treatment with avelumab or other immunotherapeutics. Samples will also be assayed for anti-avelumab antibody using a validated analytical method. All of the samples that are positive for ADA may also undergo characterization for neutralizing antibodies (NAb).

9.1.2 Mandatory FFPE Tumor Tissue

A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow for sectioning of fifteen (15) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should provide fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If tissue from multiple surgeries is available, the most recent specimen should be submitted. Archived or de novo tumor tissue from cytologic sampling (e.g., fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted.

The FFPE block or 15 unstained slides should be mailed to the study coordinator at DFCI. Send FFPE block via overnight post to the following address:

Patrice Basada
Dana-Farber Cancer Institute
450 Brookline Ave, DA-122
Boston, MA 02215
Phone: 617-632-4792
Email contact: Patrice_Basada @DFCI.harvard.edu

9.1.3 Optional Core Biopsies for Exploratory Assessment

Collection of a de novo (i.e., new biopsy) tumor sample prior to enrollment is optional although encouraged unless clinically contraindicated. In addition, an optional de novo tumor sample is encouraged at End of Treatment regardless of the reason for treatment discontinuation (e.g. progression of disease or toxicity).

Biopsies should be obtained under radiologic or other guidance, as appropriate, per institutional procedures. A minimum of 2 and up to 3 core biopsies are requested; however, less than the goal amount of tissue is acceptable, and should be based upon the clinical judgment of the clinician performing the procedure. Biopsy cores should be placed in neutral buffered formalin and then embedded in FFPE (Formalin Fixed Paraffin Embedded) no more than 16 hours after exposure to neutral buffered formalin. Biopsies will be batched shipped to:

Patrice Basada
Dana-Farber Cancer Institute
450 Brookline Ave, DA-122

Boston, MA 02215
Phone: 617-632-4792
Email: Patrice_Basada @DFCI.harvard.edu

9.1.4 Utilization of Resected Tumor Samples for Exploratory Assessment

Collection of any fresh tumor tissue not used for direct pathological and clinical assessment or mandated for other use per existing institutional protocol for possible future assessment will be endeavored for direct studies of immune infiltrates and host-tumoral-immune dynamics.

9.2 Planned Biomarker and Correlative Studies

Planned correlative and exploratory analyses in blood, tissue and or fluid samples may include but are not limited to:

- Assessment of CD3+ tumor infiltrating lymphocytes (TILs) and circulating lymphocytes, CD8+ TILs, CD8+/CD4+FOXP3+ TIL ratio, CD137+CD8+ TILs, CD137+CD8+/CD4+FOXP3+ TIL ratio;
- Assessment of myeloid, stromal and other immunoactive cell types from blood, tissue and fluid samples;
- Assessment of the expression pre-, during, and at time of progression of immune checkpoints including TIM-3, LAG-3, CTLA-4, PD-L2, PD-L1, PD-1, IDO
- Ex vivo stimulation assays to interrogate the functional response of T-cell in the presence and absence of immunomodulatory agents;
- Whole exome sequencing (WES) for specific DNA gene repair mutations and neoantigen assessment as well as for single nucleotide polymorphisms (SNPs) in immunologically relevant genes;
- HLA-typing
- Anti-avelumab antibodies
- Multigene next generation sequencing assay (Oncopanel Assay)

Studies may entail the use of ex-vivo biopsy samples, blood and resection samples as available and will be pursued in conjunction with the Dana-Farber Cancer Institute and DNA Repair Center and the Center for Immunooncology depending on funding availability.

10 STUDY CALENDAR

Screening assessments, excluding scans and x-rays, are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Assessments must be performed prior to administration of avelumab. Study assessments and avelumab infusions (Days 1 and 15) should be administered within ± 3 days of the protocol-specified date, unless otherwise noted. For patients who are receiving talazoparib, it will be taken daily as described in section 5. For patients receiving combination avelumab/axitinib, axitinib will be taken twice daily as described in Section 5.

	Pre-Study	C1/D1	C1/D15	C2[a]/D1	C2[a]/D15	Off Treatment[b]
Avelumab		X	X	X	X	
Talazoparib*		QD				
Axitinib**		BID				
Informed consent	X					
Archival FFPE sample	X					
Demographics	X					
Medical history	X					
Concurrent Medications	X	X	X	X		
Physical exam	X	X	X	X		X
Vital signs[c]	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X	X
TSH and Free T4[h]	X	X		X		X
HBV surface antigen and HCV antibody tests[i]	X					
Urinalysis**	X	X		X		X
Adverse event evaluation	X	X	X	X	X	X
CT or MRI scan (chest, abdomen, pelvis) and Tumor assessments (RECIST 1.1)[e]	X	Tumor measurements are repeated **every 8 weeks**. Documentation (radiologic) must be provided for participants removed from study for progressive disease.				X
B-HCG[f]	X					

Urine pregnancy test[f]				X		
Research blood draw[g]		X		X		X
Optional biopsy	X					X
EKG & assessment of LVEF (MUGA or Echocardiogram)**[j]	X					

a. Cycle 2 and subsequent cycles.
b: Off-Treatment evaluation. Reassessments for toxicity, disease progression, and survival will be performed up to 30 days after last treatment dose. Participants will be followed for 3 years after removal from study or until death, whichever occurs first. Survival status should be checked every 6 months during that time.
c: Vital signs will include resting heart rate, blood pressure, temperature and weight at the screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration according to institutional practice.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. **For participants in the Avelumab/Axitinib cohort only: serum Lipase and amylase at baseline and when clinically indicated.
e: Patients will be restaged every 8 weeks [±7 days]. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment for a minimum of 1 year may have the tumor imaging assessments expanded to every 12 weeks [±7 days].
f: For women of childbearing potential: a Serum pregnancy test ≤72 hours prior to first dose of study treatment. Thereafter, a urine pregnancy test will be performed every 4 weeks while on treatment with study drug. Results of the most recent pregnancy test should be available prior to the administration of study intervention.
g: 30 mL of blood will be drawn (20 mL into two purple top [EDTA] tubes (10 mL blood per tube) and 10 mL into one red top tube) before the start of infusion on C1D1; C2D1; C3D1; and at End of Treatment,
h: Pre-study and prior to the first 2 cycles, then as clinically indicated, and at off-study visit.
i. If HCV antibody test is positive the confirmatory HCV RNA test should be done.
j. And as clinically indicated
* for participants in the avelumab/talazoparib cohort only
** for participants in the avelumab/axitinib cohort only
QD = daily
BID = twice daily

11 MEASUREMENT OF EFFECT

As noted elsewhere, measurement of effect will be assessed by both the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and by the Immune-related Response Criteria Derived from RECIST 1.1 (irRECIST).

11.1 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

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 10mm or greater when assessed by CT or MRI (slice thickness 5-8mm).
- Lesions with longest diameter at least 20mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15mm or greater when assessed by CT.

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

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9mm) 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 <10mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

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.

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, 0mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5mm should be recorded.

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

- 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 <10mm). 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 5mm.
- 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.

Non-target disease

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

New Lesions

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.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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.

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

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Determination 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.

11.2 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-CTLA-4 and anti-PD-1 / anti PD-L1 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 (Hodi *et al.*, 2008; Hoos *et al.*, 2010). 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 (Nishino et al., 2014; Wolchok et al., 2009).

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 (Nishino et al., 2012; Wolchok et al., 2009).

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST 1.1 criteria (irRECIST) (Nishino *et al.*, 2014).

For irRECIST, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1, the irRECIST criteria

- require confirmation of both progression (at the investigator's discretion) and response by imaging at least 4 weeks from the date first documented, and
- do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per 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.

irRECIST criteria are 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 non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions 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, at the investigator's discretion.

New measurable lesions: Incorporated into tumor burden (ie, 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 outlines in the following 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**	**New non-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. Increase assessed relative to nadir.
b. Response (irCR and irPR) must be confirmed by a second, consecutive assessment at least 4 weeks apart. Progression (irPD) should be confirmed at the investigator's discretion.

12 DATA REPORTING & REGULATORY REQUIREMENTS

12.1 Data Reporting

Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13 STATISTICAL CONSIDERATIONS

We propose a non-randomized, open-label, two-cohort, two-stage, phase 2 trial, of avelumab in two cohorts of endometrial cancer patients: **MSI/POLE cohort** and **MSS cohort**. We propose a two-stage design for both MSI/POLE and MSS cohorts to inform whether avelumab has significant clinical efficacy that is worth of further evaluation in each of the 2 cohorts. Furthermore, for the new MSS cohort to be treated with avelumab/talazoparib, the same two stage design will be employed to inform whether the avelumab/talazoparib combination has significant clinical efficacy that is worth of further evaluation in this (MSS) cohort.

For the MSS cohort receiving avelumab/axitinib, a two-stage Optimum design will be used to allow early stopping for futility.

13.1 Study Design/Endpoints

Primary Endpoints

To assess the activity of avelumab in patients with recurrent or persistent endometrial cancer classified by MSI/POLE genomic cohorts by evaluating the frequency of patients who survive progression-free for at least 6 months (PFS6) after initiating therapy or have objective tumor response.

Statistical considerations are developed for co-primary objectives to evaluate the objective response rate (ORR) by RECIST 1.1 and rate of progression-free survival at 6 months (PFS6), with a two-stage design that allows for early stopping for futility.

For each of the 2 cohorts (MSI/POLE vs MSS) and the new MSS cohort treated with avelumab/talazoparib a two-stage test was constructed using the method of Sill, Rubinstein, Litwin and Yothers (Sill et al., 2012) with the goal of stopping early for futility to limit patient exposure to an inactive agent while restricting the probabilities of type I and type II errors to approximately 10% and 15%, respectively. For the co-primary endpoints, a true ORR of 5% or less and a rate of progression-free survival at 6 months of (PFS6) 10% or less would not be of clinical interest (H0: $\pi_{OR} \leq 5\%$ AND $\pi_{PFS6} \leq 10\%$), whereas an improvement to a 20% objective response rate or 30% PFS6 rate would warrant further investigation of avelumab. In the first stage, 16 patients will be enrolled. If there are at least two objective responses or two patients progression-free at 6 months, accrual will continue to the second stage where an additional 19 patients will be enrolled. If at the end of the trial there are at least 4 treated patients with an objective response or 8 patients progression-free at 6 months, avelumab will be considered worthy of further study in the corresponding cohort.

Specifically, analysis of historical data (GOG129 and GOG229 series) based on similar population of patients with endometrial cancer where the levels of activity were believed to be inactive to modestly active shows that an unacceptable rate for objective response π_{OR} is 5% and for PFS6 (π_{PFS6}) is 10%, respectively. A bivariate test of the co-primary endpoints is constructed as follows:

$$H0: \ \pi_{OR} \leq 5\% \ \text{ AND } \ \pi_{PFS6} \leq 10\%$$
$$\text{vs.}$$
$$H1: \ \pi_{OR} > 5\% \ \text{ OR } \ \pi_{PFS6} > 10\%$$

Targeted alternative hypothesis: An absolute improvement in the rate of OR by 15% or PFS6 by 20% would be of clinical interest. Power is determined under two specific hypotheses (Hr: π_{OR} = 20%, π_{PFS6}= 10%) and (Hs: π_{OR} = 5%, π_{PFS6} = 30%) where sufficient activity is seen in only each endpoint, respectively. Sample size is selected to have sufficient power to reject the null under cases that assume either (a) independence or (b) dependence among the co-primary endpoints. The decision rules and operating characteristics of the two-stage design are summarized in the Table below:

Table: Decision rules and operating characteristics of the two-stage design

	Endpoint	Objective Response	PFS6
	Null hypothesis	5%	10%
	Alternative hypothesis	20%	30%
Stage 1	Number of patients	16	
	Minimum number of events to continue to Stage 2	2	2
	PET (Independence)	0.417	
	PET (Dependence)	0.502	
Stage 2	Number of patients	35	
	Minimum number of events to reject the null hypothesis	4	8
	alpha (Independence)	0.098	
	alpha (Dependence)	0.088	
	Power (Independence)	0.889	0.873
	Power (Dependence)	0.846	0.862

Similarly, using the same statistical design, for the new MSS cohort to be treated with avelumab/talazoparib, in the first stage, 16 patients will be enrolled. If there are at least two objective responses or two patients progression-free at 6 months, accrual will continue to the second stage where an additional 19 patients will be enrolled. If at the end of the trial there are at least 4 treated patients with an objective response or 8 patients progression-free at 6 months, avelumab/talazoparib will be considered worthy of further study in the MSS cohort.

For the MSS cohort receiving avelumab/axitinib, similar statistical considerations were used to evaluate the co-primary objectives ORR and PFS6. This cohort will be evaluated using a two-stage test constructed using the method of Sill, Rubinstein, Litwin, and Yothers (Sill et al, 2012), with the goal of stopping early for futility to limit patient exposure to an inactive agent while restricting the probabilities of Type I error to 10% and Type II error to 15%. This is derived from historical data (the GOG 129 and GOG 229 series) based on a similar patient population where the levels of activity believed to be inactive to modestly active showed that an unacceptable rate for ORR π_{OR} is 5% and for PFS6 (π_{PFS6}) is 10%, respectively. A bivariate test of the co-primary endpoints is constructed as follows:

$$H0: \ \pi_{OR} \leq 5\% \quad AND \quad \pi_{PFS6} \leq 10\%$$
$$vs.$$
$$H1: \ \pi_{OR} > 5\% \quad OR \quad \pi_{PFS6} > 10\%$$

For the co-primary endpoints, a true ORR of 5% or less and a rate of progression-free survival at 6 months (PFS6) of 10% or less would not be of clinical interest (H0: πOR $\leq$ 5% AND πPFS6 $\leq$ 10%), whereas an improvement to a 20% objective response rate or 30% PFS6 rate would

warrant further investigation of axitinib/avelumab.

Using these parameters, in the first stage, 16 patients will be enrolled. If there are at least 2 objective responses or 2 patients progression-free at 6 months, accrual will continue to the second stage where an additional 19 patients will be enrolled. If at the end of the trial there are at least 4 treated patients with an objective response or 8 patients progression-free at 6 months, axitinib/avelumab will be considered worthy of further study.

13.2 Sample Size, Accrual Rate and Study Duration

The planned total sample size is a maximum of 105 patients. The total sample size will be adjusted to allow for replacement of participants who never began protocol therapy for reasons including ineligibility, inevaluability, and participant drop out. While the maximum target accrual is 105 patients, up to 115 patients can be enrolled to allow for replacement. The planned maximum sample size for the MSS cohort receiving avelumab/talazoparib will be 35 patients (16 for the first stage and 19 for the second). Based on the accrual of the previous MSS cohort, we estimate a monthly accrual of 4-5 patients. Patients will be followed for a maximum of 3 years.

For the MSS cohort receiving avelumab/axitinib, the planned maximum sample size will be 35 patients (16 for Stage 1 and 19 for Stage 2). We anticipate enrollment to the first stage to be completed within 2-3 months, based on enrollment of the previous cohorts using avelumab alone and combination avelumab/talazoparib. The duration of the study will depend on whether the study will move to the second stage.

The planned enrollment report is shown in the following Table.

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	15	0	0	0	**15**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	7	0	3	0	**10**
White	69	0	11	0	**80**
More Than One Race	0	0	0	0	**0**
Total	**91**	**0**	**14**	**0**	**105**

13.3 Stratification Factors

Participants will be classified into one of two cohorts of recurrent or persistent endometrial cancer of any histology:

a. **The first cohort (MSI/*POLE* cohort) includes endometrial cancers that are:**

MSI-H as determined by immunohistochemical complete loss of expression (absence of nuclear immunoreactivity) of at least one of the mismatch repair genes MSH2, MSH6, MLH1 and PMS2. This test is now done routinely for every newly diagnosed endometrial cancer patient in most centers in the US.

And/OR:

POLE*-mutated**, i.e. endometrial cancers known to harbor mutations in the exonuclease domain of polymerase e (POLE***) as determined by targeted sequencing or other next generation sequencing assay.

b. **The second cohort (MSS cohort) includes:**

Endometrial cancers that are **MSS** as determined by normal immunohistochemical nuclear expression of all the mismatch repair genes MSH2, MSH6, MLH1 and PMS2. Tumors which have not been sequenced for POLE mutations (i.e. their POLE mutations status is unknown) but are MSS, will be included in this cohort.

13.4 Analysis of Secondary Endpoints

The distributions of progression-free- and overall survival times in each cohort will be estimated by using Kaplan-Meier analysis. Immune-related objective response rate for each cohort will be estimated as described in Section 11.2. Immune-related progression-free survival (irPFS) rate for each cohort is defined as time from cohort assignment to death or to immune-related progression of disease (irPD) as defined in Section 11.2.

All analyses of exploratory endpoints in this study are exploratory in nature. Patients who have tumors that are amenable to biopsy will be asked to undergo pre- and posttreatment biopsies. These studies will be optional. For baseline continuous endpoint data, such as PD-L1 and CD8, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for each cohort. For baseline categorical data, the number and percentage of patients in each category will be provided by treatment arm. Appropriate statistical methods may be used to investigate any possible relationship of biomarker levels with avelumab anti-tumor efficacy in each cohort.

13.5 Reporting and Exclusions

13.5.2 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.5.3 Evaluation of the Primary Efficacy Endpoint

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following 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). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.
All participants 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. Participants in response categories 5-9 will not be considered evaluable but will remain within the intention to treat analysis.

Patients who develop brain metastasis on study, but continue on study after definitive treatment of their cranial disease, will be considered to have had progressive disease at the point of the diagnosis of the initial brain metastasis.

All conclusions should be based on all evaluable participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14 PUBLICATION PLAN

Publication guidelines exist within the DF/HCC Gynecologic Oncology Program. The study principal investigator will be responsible for collection of data, interpretation of data, monitoring of toxicities, and publication of abstracts and final manuscripts. The principal investigator chooses the different authorship slots per the DF/HCC gynecologic oncology program guidelines.

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX B*:* DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc.) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Office of Data Quality: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, **Panagiotis A. Konstantinopoulos, MD,** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials).

- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC ODQ.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the

Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.

- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration

Refer to Section 4 of the protocol for the participant registration process.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.9.2 Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC ODQ develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web-based training for eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.1.5 and 8.2.5.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. At a minimum, the DF/HCC Lead Institute, or designee, will monitor each participating site twice a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in Coordinating Center initiated teleconferences, as scheduled. The Coordinating Center will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition,

upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments, provided that the minimum monitoring frequencies are adhered to.

Remote Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

A minimum of 3 participants per site annually is recommended for Phase II trials. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, and DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.