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Title: A phase 2 clinical trial of Axitinib and Avelumab in patients with recurrent/metastatic adenoid cystic carcinoma (ACC)

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1. Introduction

1.1 Background and Rationale

Approximately 1,200 new cases of adenoid cystic carcinoma (ACC) occur each year in the United States. ACC is the second most common malignant salivary gland tumor with a recurrence rate following curative intent treatment of 40-50%. ACC is overall chemotherapy-refractory and there is no standard of care treatment for patients with recurrent/metastatic disease, highlighting the urgent need for effective therapy for this patient population. While the majority of patients have indolent metastatic disease, which eventually "accelerates", approximately 15% have NOTCH1 activating mutations which drives a very aggressive disease phenotype and shorter survival.

VEGF is highly expressed in ACC and its overexpression correlates with tumor aggressiveness. VEGFR inhibitors have shown modest activity in ACC as single agent, rendering response rates of approximately 5 to 10% and disease stability in a large proportion of patients. Given most metastatic ACC have an indolent course, the clinical benefit of disease stability is questionable if disease progression in a pre-specified timeframe is not documented.

In a phase II single arm study including 33 ACC patients, axitinib led to objective responses in 9% of patients, disease stability in 75.8% (30% for more than 6 months), and 67% of patients had tumor shrinkage. In this study, evidence of disease progression by imaging within 6 months of study enrollment or worsening disease-related symptoms was required inclusion criteria.
Immune profiling of ACC samples revealed that most tumors express PD-L2 but have few infiltrating immune cells. Pembrolizumab single agent is being studied in salivary gland carcinomas in a phase 1b trial (Keynote-028) and no responses were seen in ACC.

VEGF-A reduces adhesion molecule expression on endothelial cells, which results in a dysfunctional tumor vasculature and inhibits the infiltration of T cells and other immune cells into the tumor. Several studies have shown an association of tumor angiogenesis or elevated VEGF-A levels with reductions in tumor T cell infiltration. VEGF-A can also suppresses dendritic cell differentiation and activity, increases the expression of checkpoint molecules on CD8 T cells, and modulates the proliferation of regulatory T cells. Treatment of mouse models with VEGFRs inhibitors increases T cell recruitment and infiltration into tumors and can be synergistic with anti-PD1.

Preliminary safety and efficacy results from an ongoing phase Ib study of axitinib plus pembrolizumab in treatment-naïve patients with renal cell carcinoma have been recently presented. Out of 52 enrolled patients, 35 (67.3%) had an objective response: 2 had complete response and 33 had partial responses; 11 patients had stable disease. Only 10 patients tested positive for PD-L1.
A phase 1b dose-finding study of avelumab and axitinib in patients with advanced renal cell carcinoma revealed the recommended phase 2 dose to be the standard 10 mg/Kg of avelumab intravenously every 2 weeks and axitinib 5 mg per oral twice a day. All 6 patients enrolled had clinical benefit, and five out of six (83%) achieved a partial response (PR). A phase III clinical trial with this combination is ongoing in metastatic renal cell carcinoma (NCT02684006). To put these

results in perspective, in a large phase III trial, axitinib single agent in first line for metastatic renal cell carcinoma rendered an ORR of 32%. Based on this data, we believe that the combination of axitinib and avelumab will be well tolerated and enhance anti-tumor response of axitinib single agent in patients with incurable ACC who are actively progressing. Given the high unmet need, if promising, the results of this trial could lead to a definitive study that can establish the first standard of care systemic therapy for patients with recurrent/metastatic ACC.

1.2 Avelumab

Avelumab is a fully human anti-PD-L1 mAb of the Ig G1 isotype that is currently being investigated in combination with other cancer immunotherapies to enhance anti-tumor activity over that expected by avelumab alone in patients with locally advanced or metastatic solid tumors. Avelumab is expected to increase the effectiveness of anti-tumor T cells by preventing inhibition of T cell activation. This effect is expected to be enhanced by agents that promote anti-tumor immunity by complementary mechanisms such as promotion of T cell survival or removal of inhibitory myeloid cells.
Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death protein-1 (PD-1). Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells and therefore expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death-ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.

1.2.1 Avelumab Clinical Experience

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in Phase 1, 2, and 3 clinical protocols in a wide variety of cancers, including non-small cell lung cancer, gastric cancer, Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), ovarian cancer, urothelial cancer, and Hodgkin's Lymphoma, as single agent or in combination with chemotherapy, tyrosine kinase inhibitors (TKIs), or other immune-modulating agents. The safety profile of avelumab administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in MCC (N=88). Study EMR100070 001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor indications. As of 09 June 2016, a total of 53 patients were treated in the dose escalation phase of the EMR100070-001 study, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg, respectively. None of the patients treated with doses up to 10 mg/kg experienced a dose limiting toxicity (DLT), and the 10 mg/kg dose of avelumab was thus considered a safe and well tolerated dose for further investigation in the dose expansion cohorts. One DLT (a Grade 3 immune related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg. The dose expansion phase of study EMR100070-001 included patients with NSCLC, gastric cancer, breast cancer, colorectal cancer, castration resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, RCC, and SCCHN. Study EMR100070-003 Part A was conducted in patients with MCC. A summary of pooled safety data (N=1738) from the expansion phase of study EMR100070-001 and study EMR100070-003 is provided here. Treatment emergent adverse events

(TEAEs) were observed in 1697 (97.6%) patients, with the most frequent (□10%) being fatigue (32.4%), nausea (25.1%), diarrhea (18.9%), constipation (18.4%), decreased appetite (18.4%), infusion related reaction (17.1%), weight decreased (16.6%), vomiting (16.2%), anemia (14.9%), abdominal pain (14.4%), cough (13.8%), pyrexia (13.6%), dyspnea (13.2%), edema peripheral (11.9%), back pain (11.8%), and arthralgia (10.4%). Treatment related TEAEs were observed in 1164 (67.0%) patients, and the most frequent (>0.5%) were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%). A total of 177 patients (10.2%) experienced Grade ≥3 treatment related TEAEs, and the most frequent (≥0.5%) were fatigue (1.0%), lipase increased (1.0%), gamma-glutayml transferase (GGT) increased (0.6%), infusion related reaction (0.6%), and asparatate aminotransferase (AST) increased (0.5%).

A total of 777 (44.7%) patients had at least 1 serious TEAE. Treatment related serious TEAEs were reported in 108 (6.2%) patients, with the most frequent (≥0.2%) being infusion related reaction (0.9%), pneumonitis (0.6%), pyrexia (0.3%), adrenal insufficiency (0.3%), and hypothyroidism, diarrhea, vomiting, autoimmune disorder, autoimmune hepatitis, transaminases increased, dyspnea, and colitis (0.2% each). There were 911 deaths (52.4%) in the pooled safety data set. The majority of deaths were due to progressive disease (42.8%). There were 59 (3.4%) deaths attributed to TEAEs not related to trial treatment, and 4 deaths (0.2%) attributed to a treatment related TEAE by the investigator and which occurred up to 30 days after the last dose of avelumab: pneumonitis (1 case), acute liver failure (1 case), respiratory distress (in the context of sepsis) (1 case), and autoimmune hepatitis with hepatic failure (1 case). In addition, 1 patient died with acute respiratory failure (in the context of lung cancer progression) considered related to avelumab by the investigator 37 days after the last dose of avelumab. The cause of death was marked as “other” or “unknown” in 17 (1.0%) and 83 (4.8%) of cases, respectively.

A total of 244 patients (14.0%) permanently discontinued avelumab treatment due to TEAEs, including 107 patients (6.2%) discontinuing because of treatment related TEAEs. The most frequent treatment related TEAEs leading to treatment discontinuation were infusion related reaction (1.8%), GGT increased (0.4%), and diarrhea, fatigue, autoimmune disorder, alanine aminotransferase (ALT increased), blood creatine phosphokinase (CPK) increased, lipase increased, arthralgia, and pneumonitis (0.2% each).

Immune related adverse events (irAEs): in the pooled safety data (N=1738), a total of 247 patients (14.2%) experienced irAEs, defined as adverse events requiring use of corticosteroids (and/or hormonal therapy for endocrinopathies), and no clear alternate etiology. The median time to first onset of an irAE was 11.7 weeks. The most frequent irAEs were thyroid disorders including hypothyroidism (5.2%), hyperthyroidism (0.4%) and thyroiditis (0.2%), immune-related rash (5.2%), immune-related colitis (1.5%), immune related pneumonitis (1.2%), immune-related hepatitis (0.9%), adrenal insufficiency (0.5%) and immune-related myositis (0.5%). In addition, irAEs reported in 0.1% of patients in the pooled safety dataset included: type 1 diabetes mellitus, immune-related nephritis/renal dysfunction, hypopituitarism, uveitis and Guillain-Barre Syndrome. The majority of irAEs were Grade 1 or Grade 2 in severity, with 39 (2.2%) being of Grade ≥3 severity. Fatal outcome was reported in 1 patient (0.1%) with immune-related pneumonitis, and 2 patients (0.1%) with immune-related hepatitis. Other relevant irAEs reported with avelumab outside the pooled safety dataset included 1 case of fatal immune-related myocarditis in study B9991002 (avelumab in combination with axitinib for RCC), 1 case of non-fatal immune related myocarditis in the 20 mg/kg

cohort of the dose escalation phase of Study EMR100070-001, and 2 patients with non-fatal graft versus host disease (GVHD) in study B9991007 (avelumab in patients with classical Hodgkin's lymphoma).

Infusion Related Reactions (IRRs): a total of 439 patients (25.3%) experienced at least 1 infusion related reaction, defined as a TEAE coded under the Preferred Terms (PTs) of infusion related reaction, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, and abdominal pain according to a predefined case definition. The most common PTs that met the definition for an IRR included: infusion related reaction (17.0%), chills (5.4%), and pyrexia (3.6%).

Most of the events were of Grade 1 or Grade 2 severity. Grade ≥3 infusion related reactions occurred in 12 patients (0.7%) including 3 patients (0.2%) who experienced Grade 4 IRRs. No Grade 5 IRRs were reported. In most cases, the first occurrence of an IRR was related to the first infusion, with only 6 patients experiencing the first IRR at the fifth or later infusion. All Grade ≥ 3 IRRs occurred with the first (7 patients) or second (5 patients) infusion. Overall, 21.6% of patients had 1 IRR, 2.6% of patients had 2 IRRs, 14 patients (0.8%) had 3 IRRs, and 3 patients had > 3 IRRs. IRR recurrence after the fourth infusion was rare (15 patients) and all recurrent IRRs were of Grade 1 or 2 severity. In 35 patients (2.0%), treatment was permanently discontinued because of an infusion related reaction.

Immunogenicity of Avelumab in Humans: Based on the Phase 1/1b Trial EMR 100070-001, the incidence of anti-drug antibodies (ADAs) was relatively low, with 1 out of 39 patients (2.6%) in the dose escalation cohorts and 10 out of 338 patients (2.9%) in a non-small cell lung cancer (NSCLC) expansion cohort. In 8 of these 10 patients, a positive signal was observed at a single time point and a decrease in avelumab serum exposure was observed in the 2 patients with multiple positive samples. From these 11 positive patients, 2 patients had symptoms on the day of the infusion compatible with an immune reaction (chills and fever, nausea and vomiting) and, therefore, these AEs could be ADA related. For the other 9 ADA-positive patients, no such AEs were recorded.

1.2.2. Pharmacokinetics of Avelumab in Humans

Avelumab PK and dose proportionality following the first 1-hour infusion have been characterized in 77 Caucasian patients treated in the dose escalation and expansion cohorts of
Study EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of maximum plasma concentration (Cmax) and area under the curve (AUC) increased in a dose proportionate fashion for the 10 and 20 mg/kg doses. The half-life of avelumab tended to increase with dose, likely due to target mediated disposition at lower doses (1 mg/kg and 3 mg/kg), but terminal half-life of 10 mg/kg (102 +/-28 hours) and 20 mg/kg (120 +/-42 hours) doses were similar, taking into account the PK variability. This likely indicates target mediated elimination does not increase at these two doses and target occupancy is very high.

Target occupancy on peripheral blood CD3+ T-cells was investigated in human blood in vitro by flow cytometry after spiking of whole blood samples from 8 healthy volunteers with avelumab over a concentration 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 with a plateau indicating at least 95% receptor occupancy reached in all blood samples at 1 µg/mL.

PK profiles obtained from 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 (C_{trough}) at the end of the first cycle after administration of the 10 mg/kg dose is 21 +/-12 µg/mL (n=283). This median C_{trough} increases during the subsequent cycles to 25 +/- 16 µg/mL (second cycle) (n=269), 27 +/-17 µg/mL (third cycle) (n=202), and remains between 27 and 36 µg/mL during the subsequent cycles (n=55–171).

1.3 Axitinib

Axitinib is an oral, potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. As of 22 September 2014, axitinib has been approved in over 65 countries for advanced renal cell carcinoma (RCC) after treatment with one prior systemic therapy; the actual indication varies from country to country. The safety and efficacy of axitinib is being evaluated in subjects with a variety of solid tumors, including in treatment-naïve subjects with advanced RCC.

1.3.1 Axitinib clinical experience

The table below summarizes the most common treatment-emergent all-causality AEs reported in ≥10% cancer subjects who received single agent axitinib. The majority of subjects (98%; 1445/1474) reported at least one AE (all grade) and 73.7% (1086/1474) reported at least one grade ≥3 AE.

For single-agent axitinib, the most common treatment emergent all causality AEs reported from 1474 cancer subjects were: diarrhea 55.0%, hypertension 51.0%, fatigue 47.1% , decreased appetite 40.0% , nausea 32.6% ,weight decreased 32.2% , dysphonia 31.1% , palmar-plantar erythrodysaesthesia syndrome 29.4% , hypothyroidism and vomiting 22.6% , constipation 20.3% , proteinuria 20.1% . The most frequent Grade ≥3 events were: hypertension 20.7%, fatigue 10.2%, and diarrhea 10.1%.

Table. All-causality adverse events reported in ≥10% patients who received single agent axitinib

Table 1

Preferred Event Term MedDRA (v.17.0)	Axitinib N=1474	
	Grade ≥3 n (%)	All Grades n (%)
Any AEs	1086 (73.7)	1445 (98.0)
Diarrhoea	149 (10.1)	810 (55.0)
Hypertension	305 (20.7)	752 (51.0)
Fatigue	151 (10.2)	694 (47.1)
Decreased appetite	68 (4.6)	590 (40.0)
Nausea	33 (2.2)	481 (32.6)
Weight decreased	87 (5.9)	474 (32.2)
Dysphonia	5 (0.3)	459 (31.1)
Palmar-plantar erythrodysaesthesia syndrome	104 (7.1)	433 (29.4)
Hypothyroidism	4 (0.3)	333 (22.6)
Vomiting	32 (2.2)	333 (22.6)
Constipation	8 (0.5)	299 (20.3)
Proteinuria	59 (4.0)	296 (20.1)
Cough	12 (0.8)	285 (19.3)
Headache	15 (1.0)	285 (19.3)
Dyspnoea	65 (4.4)	269 (18.2)
Arthralgia	27 (1.8)	246 (16.7)
Abdominal pain	39 (2.6)	239 (16.2)
Back pain	38 (2.6)	239 (16.2)
Stomatitis	24 (1.6)	231 (15.7)
Pain in extremity	22 (1.5)	221 (15.0)
Rash	7 (0.5)	216 (14.7)
Asthenia	60 (4.1)	201 (13.6)
Mucosal inflammation	17 (1.2)	194 (13.2)
Dyspepsia	1 (0.1)	178 (12.1)
Abdominal pain upper	13 (0.9)	166 (11.3)
Dizziness	11 (0.7)	157 (10.7)
Disguesia	0 (0)	148 (10)

As of 30 June 2013, a total of 1063 subjects received axitinib in combination with other anticancer drug(s) including docetaxel, carboplatin/paclitaxel, gemcitabine, gemcitabine/cisplatin, paclitaxel, capecitabine, FOLFIRI, FOLFOX, FOLFOX plus bevacizumab, and pemetrexed/cisplatin. Of these 1063 subjects, 381 with pancreatic cancer received axitinib plus gemcitabine in studies A4061016 and A4061028. The other 682 subjects received axitinib in combination with various anticancer treatments (see Section 5.2.4.2) in studies A4061010 (breast cancer), A4061019 (solid tumor), A4061020 and A4061034 (colorectal cancer; CRC), A4061030, A4061038, A4061039 (NSCLC), and A4061055 (gastric cancer). Across all combination studies 97.1% (1044/1075) of subjects reported at least one AE. The most common treatment-emergent, all causality AEs reported were: nausea (53.1%), fatigue (49.8%), diarrhea (46.6%), decreased appetite (42.7%), hypertension (40.7%), vomiting (37.0%), neutropenia (32.4%), constipation (29.3%), headache (21.2%), abdominal pain (20.7%), asthenia (20.6%), and stomatitis (20.4%).

1.3.2. Pharmacokinetics of axitinib in Humans

The dose proportionality of axitinib has been evaluated at steady state following multiple dosing with total daily doses from 2 to 40 mg. The plasma pharmacokinetics of axitinib at steady state is generally linear. In the first in human (FIH) Phase 1 study A4060010 in patients with solid tumors, the geometric mean AUC0-24 on Day 15 was 261, 458, and 971 ng.h/mL for 5 mg BID, 15 mg QD, and 20 mg BID dosing cohorts respectively, which represents AUC(0-24) increments of 1: 1.8 : 3.7 for dose increments of 1 : 1.5 : 4, respectively (a proportional increase in AUC(0-24) per dose increment). In Phase 1 study A4061019 in patients with solid tumors, the geometric mean AUC0-24 estimates were 47.8, 198 and 382 ng.hr/mL for 1 mg BID, 3 mg BID and 5 mg BID doses respectively, indicating that doses were proportional from 3 to 5 mg BID but were more than proportional from 1 to 3 mg BID; an explanation for this observation may be the small number of patients (n=3) at the 1 mg dose.

Axitinib is rapidly absorbed with maximal plasma concentrations generally occurring within the first 4 hours following oral administration. Axitinib is orally bioavailable; in healthy volunteers, the mean absolute bioavailability was 58%.

A pilot food-effect evaluation was conducted with axitinib polymorph Form IV wet granulation tablets in 9 cancer patients in the FIH Phase 1 study (A4060010) which indicated that higher peak plasma concentrations and exposures were obtained following overnight fasting versus the fed state. A definitive food effect study (A4061006) was subsequently conducted in 42 healthy volunteers (with axitinib polymorph Form IV wet granulation tablets). The study results indicated that lower plasma exposures were obtained in the fed state versus overnight fasting state; Cmax and AUC0-∞ were reduced 39% and 23%, respectively in the fed state compared to overnight fasting. Since it was considered impractical for patients to be 'overnight fasted' around each of the 2 daily doses of axitinib and to avoid fluctuations in plasma exposures between morning and evening doses of the drug, ongoing studies at the time recommended subjects to take axitinib in the fed state. Most recently, a definitive food effect study (A4061053) for polymorph Form XLI (commercial formulation) was conducted in healthy volunteers. Overall, there were no clinically significant changes in axitinib plasma exposure or Cmax in the presence of food; the results indicated a mean 19% increase in AUC0-∞ with a high fat meal compared to overnight fasting and a mean 10% decrease in AUC0-∞ with a moderate fat meal compared to overnight fasting was observed.

Metabolism of axitinib is primarily mediated by the CYP3A4 drug-metabolizing enzyme, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1 as determined from in vitro studies with human liver microsomes. Since axitinib is predominantly metabolized by CYP3A, an interaction study with ketoconazole, a potent CYP3A inhibitor, was conducted in 35 healthy volunteers (A4061004). There was a 2-fold increase in plasma exposures of axitinib in the presence of ketoconazole and a 1.5-fold increase in peak plasma concentration (Table 6.1-5); this indicates that the upper limit for elevations in plasma concentrations of axitinib following potent metabolic inhibition following a 5-mg dose is approximately 2-fold.

1.4 Safety of Avelumab and axitinib combination

The safety of Avelumab and axitinib combination was studied in the JAVELIN Renal 100 study which is an open-label, multicenter, dose-finding, and dose-expansion, phase 1b study, done in 14 centers in the USA, UK, and Japan. 55 patients were enrolled. Six were enrolled in the dose-finding phase of the study and 49 were enrolled into the dose-expansion cohort (ten were assigned to a 7 day lead-in with axitinib therapy before the first cycle of combination therapy and 39 started combination

therapy directly per protocol. Patients in the dose-finding cohort received a median of 32·5 avelumab infusions (IQR 31·0–37·0) during a median follow-up of 69.7 weeks (IQR 66.1–74.1). The median duration of treatment was 66.6 weeks (IQR 66.0–74.1) with axitinib and 66·0 weeks (IQR65.6–74.0) with avelumab. Among the six patients in the dose-finding cohort, four (67%) had a grade 3 or 4 treatment-related adverse event (grade 3 hypertension, palmar-plantar erythrodysaesthesia, proteinuria, and mucosal inflammation and grade 4 increase in lipase concentration). One patient had a dose-limiting toxicity (grade 3 proteinuria) that led to axitinib dose reduction and resolved without sequelae; this patient continued treatment with avelumab at 10 mg/kg and 3 mg axitinib twice daily. One patient discontinued axitinib due to grade 3 palmar-plantar erythrodysaesthesia syndrome. This patient continued treatment with avelumab monotherapy until disease progression. At the end of the dose-finding phase, the maximum tolerated dose established for the combination was avelumab 10 mg/kg every 2 weeks and axitinib 5 mg twice daily. There was no differences in antitumor activity or safety between patients in either phase who received lead-in treatment with axitinib and those who did not. At the cutoff of April 13, 2017, the median follow-up for all 55 patients was 52·1 weeks (IQR 37·4–56·1). 54 (98%) patients received avelumab and axitinib, and one patient received only axitinib because of an adverse event (grade 3 increase in blood creatine phosphokinase concentration) that arose before avelumab was started. At the time of cutoff, combination treatment was ongoing in 29 (53%) of 55 patients, two (4%) were receiving treatment with axitinib alone, and one (2%) was receiving avelumab alone. Patients received avelumab for a median of 37.0 weeks (IQR 14·0–50·0) and axitinib for a median of 36·0 weeks (IQR 18.1–50.1). Reasons for treatment discontinuation were progressive disease (n=11 for avelumab and n=14 for axitinib), adverse events (n=7 for avelumab and n=4 for axitinib), withdrawal of consent (n=3 for both treatments), death (n=2 for both treatments), and physician's decision (n=1 for both treatments). All 55 patients experienced at least one adverse event during the trial, and 53 (96%) had one or more adverse events that were judged by the investigator to be related to avelumab or axitinib. The most frequent treatment-related adverse events (occurring in ≥10% of patients) included diarrhea, hypertension, dysphonia, fatigue, palmar-plantar erythrodysaesthesia syndrome, increased alanine aminotransferase concentration, rash, increased aspartate aminotransferase concentration, hypothyroidism, increased amylase concentration, decreased appetite, mucosal inflammation, infusion-related reactions, increased lipase concentration, and nausea. 32 (58%) of 55 patients had grade 3 or worse treatment-related adverse events and one died from treatment-related autoimmune myocarditis (confirmed by widespread myocarditis on post-mortem histopathology; viral cause was excluded). 16 (29%) of 55 patients reported infusion-related reactions, most of which were grade 1 or 2; one (2%) patient had a grade 3 infusion-related reaction and discontinued avelumab, and one (2%) additional patient had chills unrelated to treatment. 16 (29%) of 55 patients had infusion-related reactions with the first infusion, and one (2%) had three grade 2 infusion-related reactions at cycles eight, nine, and ten, but continued treatment beyond cycle ten until disease progression. 23 (42%) of 55 patients had immune-related adverse events; see appendix for adjudication criteria. The most frequent was hypothyroidism in 13 (24%) patients, and five (9%) had grade 3 or worse immune related events, which led to avelumab dose interruption in one patient (due to rash) and discontinuation of Avelumab in the other four patients. 20 (36%) of 55 patients had serious adverse events, which were judged to be treatment related in 12 (22%). Serious adverse events occurring in more than one patient were increased alanine aminotransferase concentration (n=2, deemed to be treatment related), infusion-related reactions

(n=2 related to avelumab), and presyncope, spinal cord compression, and hypoxia (all n=2, not related to study treatment). Ten (18%) of 55 patients discontinued one or both study drugs due to adverse events. Seven (13%) of 55 discontinued avelumab, with increased alanine aminotransferase concentration being the only adverse event leading to discontinuation in more than one patient (n=3 [6%]). Four (7%) of 55 patients discontinued axitinib (no events occurred in more than one patient). Six (11%) of 55 patients died before data cutoff: five (9%) due to disease progression (four after the end of treatment) and one (2%) due to treatment-related autoimmune myocarditis. 32 (58%) of 55 patients had avelumab dose delays, with duration of 7 days or longer in 25 (46%) of 55 patients. Four (7%) of 55 patients received less than 90% of the planned avelumab dose in one infusion because of adverse events: three due to infusion-related reactions (one of whom discontinued treatment) and one due to an electrocardiogram abnormality unrelated to study treatment. Axitinib was decreased at least once in 31 (56%) of 55 patients and increased at least once in ten (18%) of 55 patients. Axitinib dose reductions were due to adverse events in 28 (51%) of 55 patients, among whom the most common (in >5% of patients) were palmar-plantar erythrodysaesthesia syndrome (n=6), fatigue (n=5), hypertension (n=4), and proteinuria (n=3).

Table. Treatment-related adverse events occurring in ≥10% of patients

Table 2

	All grades	Grade 3	Grade 4	Grade 5
All events	53 (96%)	26 (47%)	5 (9%)	1 (2%)
Diarrhoea	32 (58%)	2 (4%)	0	0
Dysphonia	26 (47%)	0	0	0
Hypertension	26 (47%)	16 (29%)	0	0
Fatigue	25 (46%)	2 (4%)	0	0
PPE syndrome	17 (31%)	4 (7%)	0	0
ALT increased	16 (29%)	4 (7%)	0	0
Rash	16 (29%)	1 (2%)	0	0
AST increased	14 (26%)	1 (2%)	0	0
Hypothyroidism	14 (26%)	0	0	0
Amylase increased	13 (24%)	3 (6%)	1 (2%)	0
Decreased appetite	13 (24%)	1 (2%)	0	0
Mucosal inflammation	13 (24%)	1 (2%)	0	0
Infusion-related reaction*	11 (20%)	1 (2%)	0	0
Lipase increased	11 (20%)	1 (2%)	3 (6%)	0
Nausea	11 (20%)	1 (2%)	0	0
Arthralgia	9 (16%)	1 (2%)	0	0
Weight decreased	9 (16%)	1 (2%)	0	0
Pruritus	8 (15%)	0	0	0
Dysgeusia	7 (13%)	0	0	0
Stomatitis	7 (13%)	0	0	0
Dyspnoea	6 (11%)	0	0	0
Myalgia	6 (11%)	0	0	0
Proteinuria	6 (11%)	2 (4%)	0	0
Vomiting	6 (11%)	0	0	0
Hypophosphataemia	5 (9%)	2 (4%)	0	0
Blood triglycerides increased	4 (7%)	1 (2%)	0	0
Dehydration	3 (6%)	1 (2%)	0	0
Pain in extremity	3 (6%)	1 (2%)	0	0
Drug eruption	1 (2%)	1 (2%)	0	0
Dyslipidaemia	1 (2%)	1 (2%)	0	0
Haematoma	1 (2%)	0	1 (2%)	0
Myocarditis	1 (2%)	0	0	1 (2%)
Pulmonary embolism	1 (2%)	0	1 (2%)	0
Urticaria	1 (2%)	1 (2%)	0	0
Venous thrombosis	1 (2%)	1 (2%)	0	0

2. Study Objectives

2.1 Primary objective

Assess the objective response rate (ORR) to axitinib and avelumab combination according to RECIST 1.1 criteria (Appendix 1) in patients with recurrent or metastatic adenoid cystic carcinoma (ACC) who have evidence of disease progression within 6 months prior to study enrollment.

2.2 Secondary objectives

- Assess ORR to axitinib and avelumab combination according to irRECIST criteria patients with recurrent or metastatic adenoid cystic carcinoma (ACC)
- Evaluate median progression free survival (PFS), PFS rate at 6 months after start of treatment
- Evaluate median overall survival (OS), OS rate at 6 months after start of treatment
- Evaluate duration of response (DoR)
- Evaluate safety and toxicity

2.3 Exploratory

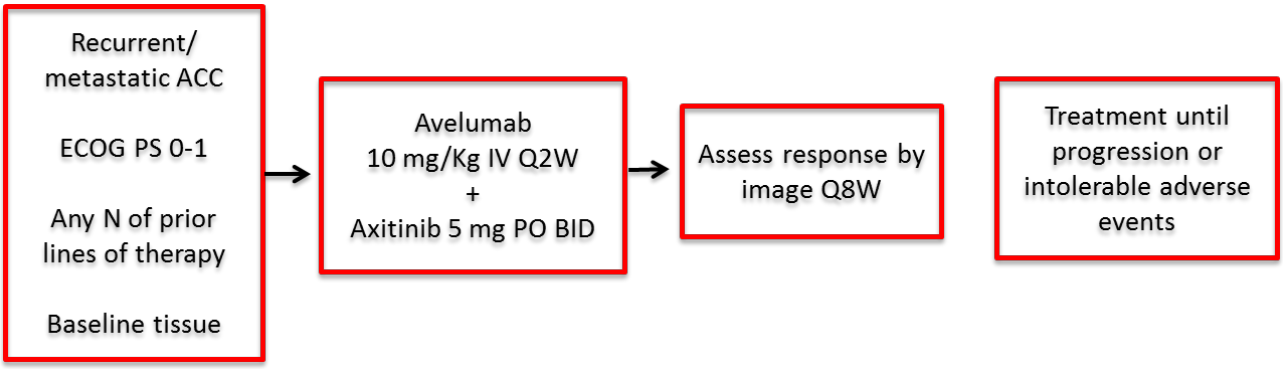
Assess molecular markers associated with response and resistance to the study combination using tissue and/or plasma obtained from study participants. We hypothesize that studying molecular characteristics of baseline tumor (such as mutational and transcriptional profile), tumor microenvironment (such as immune cells subsets) and serial plasma may reveal biomarkers associated with response to the study combination.

3. Study Design

3.1 Study Design

This is a Phase II, single center open label, study to determine the safety and efficacy of axitinib and avelumab combination in patients with recurrent or metastatic adenoid cystic carcinoma (ACC) with evidence of disease progression within 6 months prior to study enrollment.
Up to 30 patients will be treated with a combination of axitinib 5 mg orally twice a day and avelumab 10mg/kg intravenously every two weeks. A treatment cycle will be 28 days. Treatment will continue until disease progression, death, unacceptable toxicity or consent withdrawal.

3.2 Study schema



N=number; Q2W=every 2 weeks; IV=intravenously; PO= per oral; BID=twice a day; Q8W=every 8 weeks

4. Study Population

4.1 Inclusion criteria

Subjects must meet all the following criteria:

1. Male or female subjects aged ≥ 18 years
2. Eastern Cooperative Oncology Group ECOG performance status 0 or 1
3. Histologically confirmed recurrent or metastatic adenoid cystic carcinoma not amenable to curative intent surgery or radiotherapy
4. Measurable disease per RECIST 1.1
5. Evidence of disease progression within 6 months of study enrollment
6. Previously untreated subjects and subject treated with any number of prior lines of therapy are eligible
7. Adequate physiologic function defined as: Hematologic: Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused). Hepatic: Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver). Renal: Estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)

8. Must have archival tissue (Formalin-Fixed, Paraffin-Embedded (FFPE) tissue available-minimum of 15 unstained slides) or be willing to undergo a biopsy
9. For patients receiving antitherapeutic coagulation, patients must be on stable anticoagulant regimen and INR or aPTT must be ≤ 1.5 upper limit of normal.
10. Females of childbearing potential must not be breast feeding and must have a negative serum or urine pregnancy test and must agree to use highly effective contraception for a minimum of two weeks prior to receiving study medication until 30 days after discontinuation of the study medication. Acceptable methods of contraception include total and true sexual abstinence, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)), copper-banded intra-uterine devices,

and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their sexual male partner.
Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). Women will be considered post-menopausal if they have been amenorrheic for the past 12 months without an alternative medical cause. The following age- specific requirements must also apply: Women < 50 years old: they would be considered post- menopausal if they have been amenorrheic for the past 12 months or more following cessation of exogenous hormonal treatments. The levels of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) must also be in the post-menopausal range (as per the institution). Women ≥ 50 years old: they would be considered post-menopausal if they have been amenorrheic for the past 12 months or more following cessation of all exogenous hormonal treatments, or have had radiation- induced oophorectomy with the last menses > 1 year ago, or have had chemotherapy-induced menopause with >1 year interval since last menses, or have had surgical sterilization by either bilateral oophorectomy or hysterectomy. Patients should refrain from donating eggs from start of dosing until 30 days after discontinuing the study medication.
11. Non-sterilized males who are sexually active with a female partner of childbearing potential must use adequate contraception for the duration of the study and 30 days after the last dose of study medication. Adequate contraception methods include: birth control pills (e.g. combined oral contraceptive pill), barrier protection (e.g. condom plus spermicide, cervical/vault cap or intrauterine device), and abstinence. Patients should not father a child for 6 months after completion of the study medication. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing the study medication. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of the study medication.

12. For patients with hypertension, upon entry into study must have Blood pressure of <140/90

13. Qtc <470msec.

4.2 Exclusion criteria

1. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids

at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
2. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible
3. Prior organ transplantation including allogenic stem-cell transplantation
4. Active infection requiring systemic therapy
5. Known history of testing positive for HIV or known acquired immunodeficiency syndrome
6. Known history of Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
7. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines
8. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)
9. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
10. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable
11. Inadequately controlled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg). Anti-hypertensive therapy to maintain a systolic blood pressure < 140 mmHg and/or diastolic blood pressure < 90 mmHg is permitted.
12. Prior history of hypertensive crisis or hypertensive encephalopathy.
13. Patients with a baseline EKG demonstrating a QTc > 470 ms
14. Serious non-healing or dehiscing wound, active ulcer or untreated bone fracture
15. Proteinuria as demonstrated by urinalysis with microscopy > 150 mg/dL or > 1 g of protein in a 24 hour urine collection. All patients with ≥ 150mg/dL protein on urinalysis at baseline must undergo a 24 hour urine collection for protein.
16. Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
17. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
18. Subject with an uncontrolled seizure disorder, active neurologic disease, or active CNS involvement except for individuals who have previously-treated CNS metastases, are asymptomatic, and have no requirement for doses of corticosteroids (indicated to reduce brain edema) higher than the equivalent of 10 mg of oral prednisone a day or anti-seizure medication for at least 2 weeks prior to first dose of study drug.

19. History of ongoing malignancies or malignancies in remission < 2 years. Adequately curative intent treated initial stage non-melanoma skin cancers; in situ carcinoma of the cervix; breast carcinoma in situ; low-grade local bladder cancer; and low-risk prostate cancer undergoing active surveillance will be allowed.

20. Pregnant women are excluded from this study. Based on its mechanism of action. Avelumab can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG1 immunoglobulins are known to cross the placenta. Therefore, Avelumab has the potential to be transmitted from the mother to the developing fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. Therefore, potential risks of administering Avelumab during pregnancy include increased rates of abortion or stillbirth. Advise females of reproductive potential to use effective contraception during treatment with Avelumab and for at least one month after the last dose of avelumab.

21. Lactating females: There is no information regarding the presence of Avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of Avelumab due to the potential for serious adverse reactions in breastfed infants.

22. Prior treatment with anti-PD-1 or anti-PD-L1

23. Prior treatment with VEGF or VEGFR inhibitors (e.g. lenvatinib, bevacizumab)

5. Treatment Plan

Patients will be treated with a combination of axitinib 5 mg orally twice a day and avelumab 10mg/kg intravenously every two weeks. A treatment cycle will be 28 days. Treatment will continue until disease progression, death, unacceptable toxicity or consent withdrawal.

5.1 Axitinib administration

Axitinib will be given at a dose of 5 mg orally twice daily. Axitinib doses will be administered approximately 12 hours apart with or without food and at approximately the same times each day on a continuous schedule. Axitinib should be swallowed whole with a glass of water. 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. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.
The concomitant use of potent inhibitors of CYP3A4/5 should be avoided. A comprehensive list of strong CYP3A4/5 inhibitors is provided here http://medicine.iupui.edu/clinpharm/ddis/main-table/
Patients should avoid grapefruit products.
Axitinib will be provided to subjects in tablets (5 mg strength). The tablets will be packaged in appropriate packaging material and stored at room temperature.
Axitinib will be given on days 1 to 28 of a 28-day cycle.

5.2 Avelumab administration

Avelumab is a sterile, clear, and colorless solution intended for intravenous (IV) administration. It is presented with a nominal volume of 10 mL at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip off seal. The vial is intended for single use only.
Avelumab will be administered at 10 mg/kg as a 1-hour IV infusion every 2 weeks (Q2W) on Day 1 and Day 15 of each cycle.
Avelumab will be administered IV on an outpatient basis. Avelumab will 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.
In order to mitigate infusion related reactions, premedication with Diphenhydramine 50 mg IV, Acetaminophen 650 mg PO and famotidine 20 mg IV 30 to 60 minutes prior avelumab infusions is mandatory This may be modified based on local treatment standards and guidelines, as appropriate.
Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

5.3 Safety assessment

For details see section 6(study calendar and procedures)

1. Blood chemistry and hematology assessments: must be performed at screening, prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up.

2. Urine pregnancy test for women of childbearing potential must be performed at baseline and at least every month during treatment.
3. Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).
4. Extended safety follow up: give the potential risk of immune-related toxicity, safety follow up will be performed up to 90 days after the last dose of avelumab administration. The extended follow up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

5.4 Dose Modification

For overlapping toxicities (i.e., toxicities that could be attributed to either avelumab or axitinib), the study PI or co-chair will guide the study co-investigators regarding management on a case by case basis. Decision regarding which drug should be dose reduced/held will be made according to the overall incidence of the adverse event with each individual drug if other factors such as onset of symptoms cannot help define the causative agent. In general, effort should be made to continue

axitinib since single agent activity has been reported with this agent in ACC. Guidance for management of the most common overlapping adverse events are outlined below:

● Diarrhea:

Grade 1-2: manage with anti-diarrheal agents (E.g., loperamide). If no improvement dose-reduce/hold axitinib first, if no improvement hold avelumab (management as per Table 4), if improvement, axitinib can be re-started.

Grade ≥ 3: hold both drugs, discard an infectious agent, and treat with anti-diarrheal agents and steroids as per Table 4. Re-start with single agent axitinib.

● Fatigue:

Grade ≥ 2: Hold avelumab first, if no improvement dose-reduce axitinib, if improvement avelumab can be re-started. If only single agent can be tolerated, prioritize axitinib.

- Hypertension
  - Hold Axitinib when unable to control blood pressure to <140/90 on greater than 4 Blood pressure medications from multiple classes on maximally tolerated doses.

  - Qtc-Hold for Qtc>500msec, for Qtc from 470-499msec, Cardiology collaborator will evaluate and review for drug interactions and presence of underlying structural heart disease, and resume when Qtc by EKG interpretation shows normal Qtc

● Transaminitis (increase is ALT and/or AST):

Grade 1-2: Hold avelumab first, if no improvement, dose-reduce/discontinue axitinib, if improvement avelumab can be re-started

Grade ≥ 3: hold both drugs, discard an infectious agent, and treat with steroids as per Table 4. Re-start with single agent axitinib.

Other overlapping AEs:

● Decreased appetite, nausea, weight loss, vomiting, dyspnea, arthralgia, stomatitis are more common with axitinib, therefore, dose reductions of these agent should precede avelumab hold.

● Rash, hypothyroidism, asthenia and hematologic toxicities should be initially attributed to avelumab and managed accordingly (Tables 3 and 4), if no improvement by avelumab hold, axitinib dose-reduction/discontinuation should follow.

5.4.1 Avelumab

Every effort should be made to administer each of the investigational products at the planned dose and schedule. No avelumab dose modifications are permitted in this study, but the next administration of investigational product may be omitted based on persisting toxicity, as outlined in the next tables.

Table 3. Treatment Modification for Symptoms of Infusion-Related Reactions

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

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

Table 4. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**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 ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; 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.

Dermatological 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 Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.

	Consider Pulmonary and Infectious Disease consults	
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: 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 antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**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	Withhold avelumab therapy	If returns to Grade ≤ 1:

AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Increase frequency of monitoring to every 3 days.	Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 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 v4.03)	**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 arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.*	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	immunosuppressants (e.g. azathioprine, cyclosporine A).
*Local guidelines, or e.g. 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 replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate.	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.

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

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency	Permanently discontinue avelumab therapy Specialty consult	

Persistent Grade 2 or 3 irAE lasting 12 weeks or longer		

5.4.2 Axitinib dose modification

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with axitinib (and not attributable to the disease, disease-related processes for which patient is being treated, or to avelumab), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with axitinib may be restarted at the same dose or a lower dose using the rules below for dose modifications. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Table 5. Axitinib Dose interventions

Intervention	**Axitinib dose**
Starting dose	5 mg orally BID
Level -1	3 mg orally BID
Level -2	2 mg orally BID

5.4.3 Axitinib induced hypertension management

Patients will be asked to keep a home log of daily blood pressure and will be instructed NOT to take axitinib if blood pressure is > 150 x 90 mmHg with two consecutive readings and additional antihypertensives will be added to control BP to target and resume Axitinib

Management of hypertension is as follow:

Grade 1: No dose modification.

Grade 2: Withhold axitinib. Start and/or optimize anti-hypertensive therapy per institutional policy. Patient may resume axitinib after blood pressure is <150 x 90 mmHg.

Grade 3: Requires more than one antihypertensive drug or more intensive therapy than previously. If not controlled to 150x90 mmHg with medication, dose reduction required.

Grade 4: Discontinue axitinib when on4 or > antihypertensive medications and blood pressure remains >150/90 or symptoms related to hypertensive urgency.

5.5 Investigational product supplies

Avelumab and axitinib will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study site with 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 shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

5.6 Investigational product accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all investigational product supplies. Patients receiving axitinib will be required to return all unused study treatment at the beginning of each cycle. Pill count will be performed by research staff. Drug accountability will be maintained by our pharmacy team. Returned drug will be disposed of per MD Anderson institutional policy.
The study drug Supporter or designee will provide guidance on the destruction of unused investigational products (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.

5.7 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.
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 daily evaluation for excursions should be documented. 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 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 the study Supporter.
Once an excursion is identified, the investigational product must be quarantined and not used until the study Supporter provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the study Supporter approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to study Support approval will be considered a protocol deviation.
Avelumab must be stored at 2 to 8 °C or 36 to 46 °F DO NOT FREEZE

Avelumab must be allowed to reach room temperature for a minimum of 30 minutes prior to use in dose preparation. The immediate administration of the prepared solution for dosing kept at room temperature is preferred. In case the aseptically prepared dosing solution cannot be administered immediately after preparation, the acceptable holding time is: not more than 24 hours under refrigerated conditions (2-8°C, 36-46°F) with no more than 8 of those hours at room temperature (15-25°C, 59-77°F), including infusion time.
If stored under refrigerated conditions, allow each bag to equilibrate to room temperature (15-25°C, 59-77°F), preferably for one hour before administration

5.8 Preparation and administration of Avelumab

- Avelumab infusion solutions must be prepared in 0.9% Sodium Chloride (Normal Saline) and the final concentration of avelumab in the infusion solutions must be between 0.016 mg/mL to 8 mg/mL.
- Total volume of final prepared solution must be 250 mL.
- Parenteral investigational drug products must be inspected visually for particulate matter and discoloration (i.e. change in color) prior to administration, whenever the solution and container permit. If particulates or discoloration are observed, do not use the vial(s) and notify Pfizer.
- Do not shake or freeze the vial(s).
- The expiry time of final IP is 24 hours from the time the vials were removed from the refrigerator and allowed to reach room temperature: 24 hours under refrigerated conditions (2-80 C,36-460F) with no more than 8 of those hours at room temperature (15-250C, 59-770F), including infusion time. Dose preparation must be performed using sterile handling techniques in compliance with local, state, and national laws/regulations.
- Avelumab MUST be administered with a low protein binding 0.2 micron PES filter.
- Each vial is for single-use only. Each vial is for use in a single patient, for a single dose.

5.9 Treatment duration

Subjects will continue treatment until confirmed disease progression, unacceptable toxicity, refusal to participate further, or loss to follow-up. Patients with evidence of disease progression per RECIST 1.1 (see appendix 1), who were still experiencing clinical benefit could be considered for continuation of treatment as per the investigator's clinical judgment and after discussion between the investigator and study Supporter.

If patients develop unacceptable toxicity attributed to one of the study treatments leading to discontinuation, they could continue receiving the other study treatment.

6. Study Calendar and Procedures

Table 6

Required Procedures	**Screening (baseline)**	**During Treatment**	**End of Treatment/ Safety Follow-up Visit[7]**	**Long Term Follow-Up[5]**
Timing	Within 28 days prior to treatment initiation unless otherwise specified	Every 4 weeks, ± 7 days, unless otherwise specified	30 days ± 7 days after last dose of study treatment	
Consent	X[1]			
Treatment History	X			
Medical History	X			
Demographics	X			
Physical Exam	X	X	X	
Vital Signs	X	X	X	
Height	X			
Weight	X	X	X	
ECOG PS	X			
Axitinib dosing		X Twice daily		
Avelumab dosing		X every 2 weeks		
Symptoms & Toxicities	X	X On an ongoing basis throughout study	X	
Concomitant Medications	X	X On an ongoing basis throughout study	X	
Hematology Profile	X	X every 2 weeks prior to avelumab dosing	X	
Chemistry Profile[2], phosphorous[2]	X	X every 2 weeks prior to avelumab dosing	X	
GGT	X			
aPTT and INR	X			

EKG	X			
Echocardiogram	X	X[9]		
Urine analysis for proteinuria	X	X[9]		
Pregnancy Test (serum or urine) for all women of child bearing potential[3]	X	X[9]		
Radiology & Tumor Measurements [4]	X	X Every 8 weeks, ± 7 days		X
Biopsy	X If archived tissue not available			
Blood-based biomarkers	X[8]	X[8]		
Study Drug Compliance		X At each clinic visit		
Subsequent Anticancer Therapy				X
Survival Status				X

1 Written informed consent will be given by each patient prior to undergoing protocol specific evaluation and prior to receiving treatment

2 Chemistry profile includes: BUN, creatinine, sodium, potassium, carbon dioxide, magnesium, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total protein, and serum phosphorus

3 Serum or urine pregnancy test will be obtained at baseline within 7 days prior to treatment and monthly during treatment in all women of child bearing age and again if clinically indicated

4 CT scan, PET CT scan of the chest/abdomen/pelvis and/or MRI of base of skull/orbit/face as clinically indicated. CT scan or MRI of the brain if clinically indicated

5 Long term follow-up will occur every 6 months by medical/clinical data review or phone contact

6 For patients who discontinue treatment due to reasons other than disease progression, tumor assessment will continue as per during the treatment schedule (i.e. radiology & tumor measurements every 8 weeks +/- 7 days).

7 Extended safety follow up: given the potential risk of immune-related toxicity, safety follow up will be performed up to 90 days after the last dose of avelumab administration. The extended follow up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call

8 Blood will be collected on at baseline (pre-treatment), day 7 (optional), day 15, prior to C3D1, and at progression (optional).Three categories of specimen will be collected: EDTA Vaccutainer (checkpoint markers/CAFs): 10 mL = 1 x 10 mL; Streck CF-DNA BCT (ctDNA): 10 ml = 1 x 10 mL; and Sodium Heparin (immunoprofiling): 60 ml = 6 x 10 mL. All blood will be collected and processed by the Thoracic Research Team (Dr. Tran's laboratory) according the institutional and laboratory standard operating procedures (SOPs).

9 While on treatment as clinically indicated

6.1 Description of study assessments

Performance Status
The performance status of all patients will be graded according to the ECOG PS scale.

Clinical Laboratory Tests
Clinical laboratory tests will be performed to assess eligibility for enrollment and will be repeated according to study calendar included in this section. Laboratory tests can be repeated more
frequently, if clinically indicated.

Symptoms and Toxicity Assessment
The symptoms and adverse events of all patients will be graded at scheduled intervals according to the NCI CTCAE, v4.03. Patients will be monitored continuously throughout the study for the occurrence of adverse events. Planned medical interventions will not be considered an adverse event.

Radiology Assessments
CT chest (with/without abdomen/pelvis), PET-CT, and CT brain / MRI brain will be obtained according to Study Calendar included in this section. Response and progression will be evaluated in the study using the international criteria proposed by the RECIST committee, and will be performed by the MD Anderson radiology collaborator(s) on trial in a blind fashion.

7. Adverse Events Collection and reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

7.1 Definitions

7.1.1 Adverse events (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug. The term AE is used to include both serious and non-serious adverse events. For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions. The term “disease progression” should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.
Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- Pre-existing condition: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- Pre-planned or elective hospitalization: A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- Diagnostic Testing and Procedures: Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- Asymptomatic Treatment Related Lymphocytosis: This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.
- Any adverse event clearly attributable to disease progression

7.1.2 Severity criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in patient death

7.1.3 Causality (Attribution)

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Pfizer in accordance with the agreed process

- Not Related: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
- Unlikely: The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
- Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

These AEs will be reported as related if the investigator believes it is more likely than not that the investigational product caused the AE.

- Related: The AE is clearly related to use of the investigational product.

7.1.4 Unexpected adverse events

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

7.2 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

Table7

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Recommended Adverse Event Recording Guidelines	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.2.1 Serious Adverse Events (SAE) Reporting

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the institutional timeframes and procedures.

- Serious adverse events will be captured from the time of consent, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Reporting to Pfizer

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

The following reportable events must be submitted to Pfizer within 24 hours (or immediately for death or life-threatening events) using the provided Investigator-Initiated Research Serious Adverse Event Form (IIR SAE) with the Pfizer Reportable Events Fax Cover Sheet with each SAE submission.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.
- Detailed guidance on the safety reporting is provided in the Safety Reporting Reference Manual (Appendix E).

Contact information for submission of reportable events to Pfizer:

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

Or
E-mail: USA.AEReporting@pfizer.com, specifying:
PROTOCOL:
SUBJECT:
SITE/PI:
SAE/ONSET:

7.2.2 Assessment of adverse events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

7.2.3 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated Informed Consent Form (ICF) is obtained until 30 days following the last dose of study drugs or until the initiation of alternative anticancer therapy. Progressive disease should NOT be reported as an

event term, but instead symptoms/clinical signs of disease progression may be reported.
All Grade 3 – 5 adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").
All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

7.2.4 Other events requiring reporting

Overdose

An overdose is defined as a subject receiving a dose of study combination in excess of that specified in this protocol. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. The investigator will use clinical judgment to treat any overdose.

Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.
A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study combination. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant

must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.
Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study combination must be reported. Any occurrence of pregnancy must be reported per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

Paternal Exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.
To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing ends should be followed up and documented.

Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

8. Recording and Collection of Data

Case report forms

Electronic case report forms will be used for this study, stored under the Data Management Initiative (DMI) database. All data collection and storage will be performed under the DMI platform. Use of concomitant medications is routinely captured in the patient's electronic medical record and the information is readily available if it needs to be obtained for analysis of study results. As such, concomitant medications will not be captured in DMI.

9. Statistical Consideration

9.1 Definitions

All efficacy analyses will be performed in all eligible patients enrolled. Safety analyses will be performed on all patients who received any dose of any treatment.

1. Objective Response Rate (ORR) is the percent of patients whose best response is complete response or partial response as determined by RECIST 1.1 criteria.
2. irORR is the percent of patients whose best response is immune-related complete response (ir-CR) or immune-related partial response (ir-PR) as determined by irRECIST criteria.
3. Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. PFS rate at 6 months is the percentage of patients without disease progression at these time-point.
4. Overall survival (OS) is defined as the duration of time from start of treatment to death. OS rate at 6 months is the percentage of alive patients at these time-point
5. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

9.2 Analysis plan

This is a single-arm, phase II trial to assess the efficacy of the combination of axitinib and avelumab in patients with recurrent or metastatic adenoid cystic carcinoma (ACC) with disease progression within 6 months prior to study enrollment. The primary endpoint is the overall response rate by RECIST 1.1. The trial will be conducted by Simon's 2-stage design and the response rate will be estimated after the second stage (Simon, 1989).

It is assumed that the new regimen will have a target overall response rate at 6 months of 20%. A response rate of 5% or lower is considered a failure and the new regimen will be rejected under this circumstance. When the probability of accepting a "bad" regimen (i.e. ORR<=5%) is 0.05 and the probability of rejecting a "good" regimen (i.e. ORR >=20%) is 0.20, Simon's Optimal design requires to enter 10 patients in the first stage. If no patient responds to the treatment, the trial will be stopped and the regimen will be declared as ineffective. If there are one or more responses, 19 more patients will be entered in the study to reach a total of 29 evaluable patients. To ensure that we have 29 evaluable patients we will enroll a total of 30 patients. By the end of the study, the new regimen will be rejected if response rate at 6 months is less than or equal to 3/29 and will be accepted otherwise. The operating characteristics of the trial are given as follows. When the true response rate is 0.05 the probability of stopping the trial early is 60%. On the other hand, if the true response rate is 0.20, the probability to stop the trial early is 10.7%. The expected sample sizes are 17.6 and 27.0 when the true response rates are 0.05 and 0.20, respectively.

To ensure patient safety, the toxicity monitoring will be carried out from the 7^{th} patient using the stopping boundaries calculated based on the beta-binomial distribution. The target toxicity rate by the end of cycle 1 (4 weeks of treatment) is 30%. Toxicity is defined as: as adverse events in the first 4 weeks that are judged to be attributable to one agent or both in combination. Relevant hematological events are grade 4 anemia, grade 4 neutropenia lasting longer than7 days, febrile neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L with temperature >38.3°C on one measurement or ≥38.0°C for >1 h), grade 3 or worse neutropenic infection, grade 3 or worse thrombocytopenia with bleeding, or grade 4 thrombocytopenia. Relevant non-hematological

events, including those not identified by laboratory tests, were any grade 3 or worse toxicity except transient (≤6 h) grade 3 flu-like symptoms or fever that could be controlled by medical management, transient (≤24 h) grade 3 fatigue, local reaction, or headache that resolved to grade 1 or better, grade 3 or 4 nausea and vomiting controlled by optimum medical therapy within 72 h, grade 3 hypertension controlled by medical therapy, grade 3 diarrhea or grade 3 skin toxicity that resolved to at least grade 1 within 7 days of starting medical management (eg, immunosuppressants), any grade 3 or worse amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis, and tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumors; grade 3 or 4 increases in alanine aminotransferase or aspartate aminotransferase concentrations concurrent with grade 2 increase in total bilirubin concentration (liver function); non-hematological grade 3 or worse laboratory abnormality that needs medical intervention or led to hospital admission (excluding single laboratory values out of normal range judged unlikely to be related to trial treatment by the investigator, without clinical correlates, and that resolved to grade ≤1 within 7 days with adequate medical management); and any event related to the trial treatment preventing completion of at least 75% of doses of axitinib or two infusions of avelumab during the first cycle of combined therapy. The prior probability of toxicity for the regimen is modeled by a beta distribution Beta (0.3, 0.7). The following decision criteria will be applied:

$$\text{stop if Prob}\{\theta_{TOX} > 0.30 \mid \text{data from the trial}\} > 0.7$$

Patients recruited will be monitored continuously according to the following stopping boundaries for toxicity.

Table 8 Stopping Boundaries

# Patients evaluated (inclusive)	# Toxicities (inclusive) are considered too toxic
7	3-7
8-10	4-10
11-13	5-13
14-16	6-16
17-19	7-19
20-22	8-22
23-25	9-25
26-28	10-28
29	11-29
30	Always stop with this many patients

The operating characteristics are summarized in the following table.

Table 9 Operating Characteristics

True Toxicity Rate	Prob (stop the trial early)
0.1	0.032
0.2	0.225
0.3	0.584
0.4	0.876
0.5	0.982

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.1.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

Summary statistics including mean, standard deviation, median, and range for the continuous variables, and frequency tables for categorical variables, will be provided. The response rate will be estimated along with its 95% confidence interval. The distribution of time-to-event endpoints including overall survival, progression free survival and duration of response will be estimated using the method of Kaplan and Meier.

The investigator is responsible for completing an efficacy/safety summary reportThe efficacy report will be reviewed by the principal investigator and/or study co-chair. For Toxicity monitoring: This will be performed after the first 7 evaluable patients per cohort, complete 1 cycle of study treatment, and every 3 evaluable patients thereafter.

For Response assessment: After the first 10 patients and after 30 patients complete 6 months post-treatment.

A copy of the cohort summary will be placed in the Investigator's Regulatory Binder.

10. References

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Appendix 1. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.35

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.
Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.
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 < 15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

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

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/Randomization 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 post-baseline.
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 the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.
NOTE: When nodal lesions decrease to <10 mm (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 (i.e., Not Evaluable),
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 should be discussed with the radiologist and the Sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

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
< 10 mm). All target lesions must be assessed.

Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.
Stable Disease (SD): 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 (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.
Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy) with a minimum absolute increase of 5 mm.
Not evaluable (NE): Progression has not been documented, and
one or more target 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
(if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).
Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) 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.
Not evaluable (NE): Progression has not been determined, and
one or more non-target lesion sites have not been assessed; or
assessment methods used were inconsistent with those used at baseline; or
one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images); or one or more non-target lesions were excised or irradiated and have not reappeared or increased.

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.

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 PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST
When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Determination of Best Overall Response
The best overall response is the best response recorded from the start of the treatment/randomization 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 start of the treatment/randomization at a minimum interval of 6 weeks.

Appendix 2. Immune-related Response Criteria Derived From RECIST v1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics. This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1\anti PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T-cells, thus leading to tumor infiltration by T-cells and tumor regression rather than direct cytotoxic effects. 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 World Health Organization (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. 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. On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST). For irRECIST, with the exception of a complete response assessment, only target and new measurable lesions are taken into account.
In contrast to RECIST v1.1, the irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and

- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm 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 study.

irRECIST responses 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 does not meet criteria for irCR or irPR (compared to baseline), or immune-related progressive disease (irPD, compared to nadir).

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

New measurable lesions: Incorporated into tumor burden (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.

Appendix 3. ECOG Performance Status

0 Fully active, able to carry on all pre-disease activities without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work or office work

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 Dead