UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

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Official title: Single-Arm Phase II Study of Axitinib, Avelumab, and Bavituximab in Advanced HCC

NCT number: NCT05249569
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PROTOCOL NUMBER - PENDING

Single-Arm Phase II Study of Axitinib, Avelumab, and Bavituximab in Advanced HCC

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Study Drug/Treatment: Axitinib (Inlyta)
Avelumab (Bavencio)
Bavituximab

IND/IDE Number: 159270

IND/IDE Holder Name: David Hsieh, MD

Funding Source: Pfizer

NCT Number: NCT05249569

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Amended:

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Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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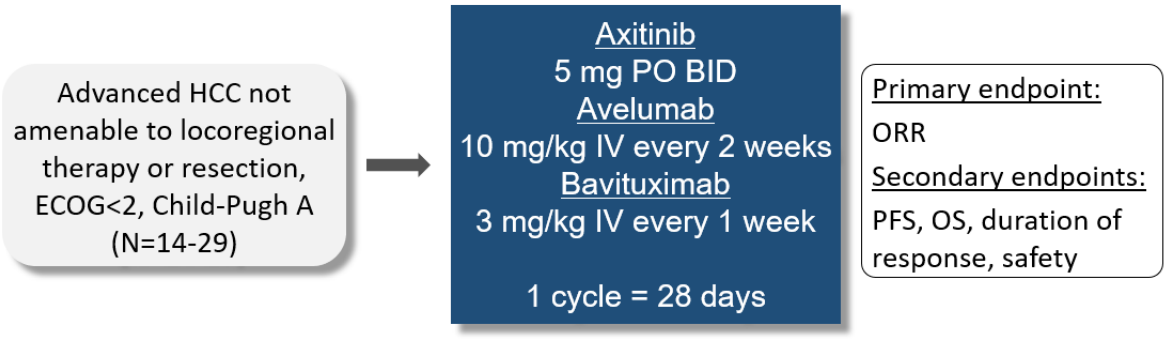


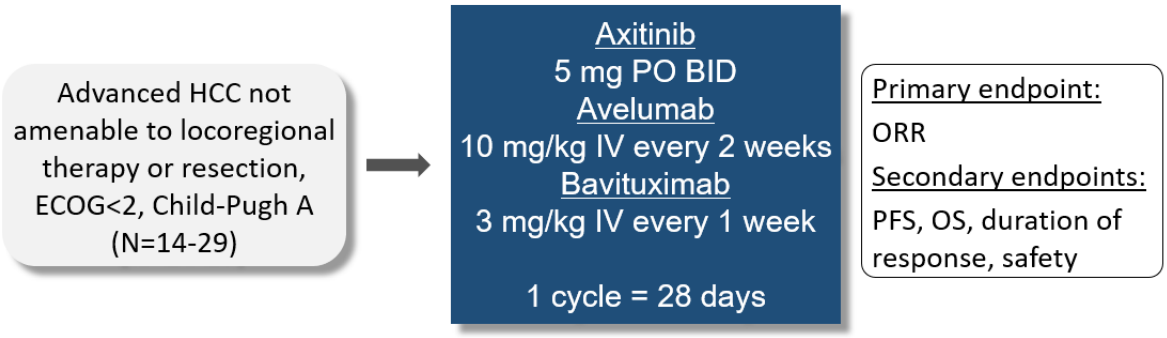
*The first 6 patients enrolled who have received at least 1 cycle of treatment will be considered a safety lead-in.

LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha Fetoprotein
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
aPTT	Activated thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BID	bis in die/twice a day
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated Antigen 4
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DR	Duration of Response
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDPE	High-Density Polyethylene
HRPP	Human Research Protections Program
HR	Hazard Ratio
ICIs	Immune Checkpoint Inhibitors
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
INR	International normalized ratio
irAEs	Immune-Related Adverse Events
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IV (or iv)	Intravenously

LD	Longest Diameter
LOAEL	Lowest-observed-adverse-effect level
MI	Molecular Intelligence
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
NOAEL	No-observed-adverse-effect level
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic
PO	peros/by mouth/orally
PR	Partial Response
PS	Phosphatidylserine
PT	Prothrombin time
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SLD	Sum of the Longest Diameter
SPGT	Serum Glutamic Pyruvic Transaminase
SVR12	Sustained Virologic Response after 12 weeks post-treatment
TK	Toxicokinetic
USP	United States Pharmacopeia
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptors
WBC	White Blood Cells

STUDY SCHEMA



*The first 6 patients enrolled who have received at least 1 cycle of treatment will be considered a safety lead-in.

STUDY SUMMARY

Title	Multi-center phase II open-label study of bavituximab, axitinib, and avelumab in advanced hepatocellular carcinoma
Short Title	Phase II study of bavituximab, axitinib, and avelumab in advanced hepatocellular carcinoma
Protocol Number	TBD
Phase	Phase 2 with safety lead-in
Methodology	Open-label
Study Duration	24 months accrual/24 months follow-up
Study Center(s)	UT Southwestern Medical Center and Parkland Health and Hospital System
Objectives	To determine the objective response rate of combination axitinib, avelumab, and bavituximab in advanced HCC not previously treated with systemic therapy.
Number of Subjects	14-29 evaluable patients
Diagnosis and Main Inclusion Criteria	1. Patients must have a histologically confirmed diagnosis of hepatocellular carcinoma; 2. No history of prior systemic therapy for HCC; 3. Patients with advanced HCC not eligible for curative and/or locoregional therapies; 4. Age ≥ 18 years; 5. Child-Pugh Score A
Study Product(s), Dose, Route, Regimen	Axitinib 5 mg PO BID Avelumab 10 mg/kg IV every 2 weeks (maximal dose of 2000 mg; 2 doses in a 4-week cycle) Bavituximab 3 mg/kg IV every 1 week (4 doses in a 4-week cycle)
Duration of administration	Study treatment will continue until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

Statistical Methodology	Safety and tolerability assessment will be performed for the first 6 evaluable patients in the safety lead-in. The primary endpoint of the trial will be objective response rate (ORR). A minimax two-stage method will be used to analyze ORR after the first 14 patients are accrued. 15 additional patients will be enrolled if 2 or more of the first 14 patients have either a complete or partial response.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

HCC is a devastating disease in the US and worldwide: Hepatocellular carcinoma (HCC) is the most common liver cancer and the fourth most frequent cause of cancer-related deaths worldwide.[1] In contrast to the decreasing disease burden of other prevalent cancer types over time, HCC incidence and related mortality continues to increase in the US and globally.[2] The increasing health burden attributed to HCC demonstrates an urgent need to develop better therapies, as many HCC patients are diagnosed beyond curative stages. In addition, because HCC often arises in the setting of cirrhosis, at-risk patients with irreversible liver injury remain at a perpetual risk of HCC. This highlights the importance of utilizing novel strategies in HCC treatment designs that may not be thwarted by known drug resistance mechanisms and are not associated with long-term sequelae.

Until recently, first-line systemic therapy for advanced HCC was limited to oral tyrosine kinase inhibitors chiefly targeting VEGF signaling. In the phase III randomized controlled SHARP trial, patients with advanced hepatocellular carcinoma (not eligible for surgical resection or transplantation) and preserved liver function (Child-Pugh A score) were randomly assigned to either systemic sorafenib or placebo.[3] Seven patients in the sorafenib group (2%) and two patients in the placebo group (1%) had a partial response, and there were no complete responses. While median overall survival was significantly prolonged with sorafenib (10.7 months in the sorafenib group and 7.9 months in the placebo group), the clinical benefit was incremental and sorafenib was associated with a greater incidence of toxicities including diarrhea and skin reactions. Nearly a decade after the FDA approval of sorafenib followed by a series of failed superiority and non-inferiority phase III trials in advanced HCC, lenvatinib gained approval for first-line treatment of advanced HCC based on the results of the phase III randomized non-inferiority REFLECT trial.[4] Patients with advanced HCC were randomized to either lenvatinib or sorafenib, and the median survival time for lenvatinib (13.6 months) was demonstrated to be non-inferior to sorafenib (12.3 months). Response rates with lenvatinib was 24.1% versus 9.2% with sorafenib, and toxicities were comparable between the two agents. Nonetheless, 57% of patients treated with lenvatinib had treatment-related treatment-emergent adverse events (AEs) of at least grade 3 and 18% had serious treatment-related treatment-emergent AEs. While both sorafenib and lenvatinib remain viable first-line options for patients with advanced HCC, the lack of progress in clinical benefit and considerable toxicities associated with oral tyrosine kinase inhibitors demonstrates an unmet need for more effective and safe HCC treatments.

Efficacy of immunotherapy in HCC:
Targeted manipulation of immune checkpoints including PD-1 and CTLA-4 using antibody-based immune checkpoint inhibitors (ICIs) can induce striking and durable clinical responses in advanced cancers. Early phase studies demonstrated that the immune checkpoint inhibitors nivolumab and pembrolizumab were associated with encouraging objective responses in HCC including cancers refractory to sorafenib.[5,6] In the phase I/II open-label, non-comparative CheckMate 040 study, patients received intravenous nivolumab 0.1-10 mg/kg every 2 weeks in the dose-escalation phase and 3 mg/kg every 2 weeks in the dose-expansion phase.[5] The objective response rate was 20% (95% CI 15-26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6-28) in the dose-escalation phase. Only three (6%) patients had treatment-related serious AEs (pemphigoid, adrenal insufficiency, liver disorder). In the phase II open-label KEYNOTE-224 study, patients who had been previously treated with sorafenib received 200 mg pembrolizumab intravenously every 3 weeks.[6] The overall response rate was 17% and 44% patients had stable disease. At the time of data cut-off, the 12-month overall

survival rate was 54%. Greater than grade 2 treatment-related AEs occurred in 26% of patients (grade 3 in 24%, grade 4 in 1%, and grade 5 in 1%).

Results from the CheckMate 040 and KEYNOTE-224 studies collectively demonstrate that immunotherapies can induce meaningful response rates in patients with HCC which are safe and durable in a subset of patients. Their distinct mechanisms of action also suggest that immunotherapies may be effective among patients previously treated with oral tyrosine kinase inhibitors. However, the phase III KEYNOTE-240 trial testing pembrolizumab versus placebo in the second line setting did not meet its primary endpoint in prolonging overall survival and progression-free survival.[7] Nonetheless, pembrolizumab was associated with a significant improvement in objective response rates (18.3% versus 4.4%) and a non-statistically significant trend towards improved survival (HR, 0.781; 95% CI, 0.611 to 0.998; P = 0.02).[8] The clinical benefit of combination immunotherapy regimens in HCC was recently demonstrated by the phase III IMbrave150 study testing atezolizumab and bevacizumab versus sorafenib in the first line setting.[8] Patients received either 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab intravenously every 3 weeks or 400 mg of sorafenib orally twice daily. Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with atezolizumab plus bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with sorafenib. These results demonstrate that while use of immunotherapy as monotherapy may be associated with modest clinical benefit, a rationally designed combination immunotherapy regimen may provide meaningful clinical activity in HCC.

1.2 Study Agents/Therapies Background and Associated Known Toxicities

1.2.1 Axitinib: Overview

Axitinib is an oral and selective inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, 2, and 3. Since 2012, axitinib has been approved by the FDA for use in patients with advanced renal cell carcinoma (RCC). In 2019, the FDA approved axitinib plus pembrolizumab or avelumab as first-line treatment for patients with advanced RCC. Given the known efficacy of targeting VEGFR activity in HCC and the established safety of combining axitinib with immunotherapies in RCC, the use of axitinib in a combination immunotherapy regimen is anticipated to be safe and active in patients with advanced HCC.

1.2.2 Axitinib: Non-clinical experience

Axitinib is a small molecule adenosine triphosphate-competitive inhibitor that binds to the unphosphorylated conformation of the catalytic domain of receptor tyrosine kinases.[9] In contrast to other VEGFR targeting agents in clinical use such as sunitinib and sorafenib which inhibit multiple receptor tyrosine kinases, axitinib is a highly specific and potent inhibitor of VEGFR1-3.[10] For instance, the concentration of axitinib that inhibits phosphorylation of VEGFR-1, -2 and -3 by 50 % (IC50) is ≈0.1, 0.2 and 0.1–0.3 nmol/L, respectively, but is notably greater at 5, 1.6 and 1.7 nmol/L for platelet-derived growth factor receptor-α and -β and stem-cell factor receptor.[11] In multiple studies, axitinib has been demonstrated to impair VEGFR effector signaling including activation of mitogen-activated protein kinases and have anti-angiogenic activity in a number of tumor models.[10,12-14]

Axitinib pharmacokinetic (PK) parameters were determined from non-Good Laboratory Practice (GLP) studies conducted in Cesarean-derived (CD)-1 mice, Sprague-Dawley rats, Beagle dogs, and cynomolgus monkeys. Axitinib demonstrated low to moderate intravenous clearance with good oral solution bioavailability, consistent with moderate absorption from the gastrointestinal tract. The unbound fraction of axitinib in plasma determined by equilibrium dialysis was 3.0%, 1.9%, 2.0%, and 0.5% in the mouse, rat, dog, and human, respectively. To assess the tissue distribution of axitinib, [^{14}C] axitinib was orally administered to pigmented male B6C3F1/Crl BR mice and assessed using quantitative whole-body

autoradiography. Radiolabeled axitinib was rapidly absorbed and well distributed into most tissues and was not associated with persistence in any organ except for the pigmented uveal tract, liver, and gall bladder. In vitro studies indicated that axitinib is metabolized in the liver by CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

1.2.3 Axitinib: Clinical experience

In a phase I, multicenter clinical trial of axitinib in patients (n = 36) with refractory tumors, the maximum tolerated dose for further phase II clinical trials was established as 5 mg bid daily.[15] Axitinib was absorbed rapidly, with peak plasma concentrations occurring within 2 to 6 hours after dosing and plasma concentrations declined with a terminal plasma half-life between 2 and 5 hours. Steady state levels were reached within 15 days, with no unexpected accumulation of drug. Principal toxicities included hypertension, fatigue, diarrhea, stomatitis, nausea, and vomiting. Hypertension was the most frequent toxicity occurring in 22 patients (61%) and in most cases (18 patients) this was controlled with antihypertensive medications. Objective responses were observed in a patient with adenoid cystic carcinoma and in 2 of 6 patients with RCC.

The safety and activity of axitinib has been evaluated in patients with HCC in 3 phase II studies. Kang et al. conducted a global, randomized, placebo-controlled phase II trial in patients with locally advanced or metastatic HCC, had Child–Pugh Class A liver disease, and progressed on or were intolerant to one prior antiangiogenic therapy. Patients were randomized (2:1) to axitinib 5 mg twice daily (n = 134) or placebo (n = 68) and the primary end point was overall survival. While axitinib was not associated with an overall survival benefit (HR, 0.907; 95% CI, 0.646; P = 0.29), progression-free survival was significantly longer with axitinib than placebo (HR, 0.618; P = 0.004) and there was a non-statistically significant trends towards greater objective responses with axitinib versus placebo (9.7% versus 2.9%; P = 0.091). The most frequent AEs reported with axitinib was diarrhea (all grades, 54%; greater than grade 3, 20%), hypertension (all grades, 54%; greater than grade 3, 26%), and hand–foot skin reaction (all grades, 34%; greater than grade 3, 15%). Laboratory abnormalities related to hepatic function were minimally or moderately increased with axitinib, demonstrating that the risk of hepatotoxicity is noticeably less in axitinib than other VEGF receptor inhibitors such as sunitinib and sorafenib.

McNamara et al. conducted a single-arm phase II trial of axitinib in patients with advanced HCC refractory to prior antiangiogenic treatments and had Child-Pugh Class A/B7 liver disease.[16] Axitinib was started at 5 mg twice daily orally, and titrated from 2 to 10 mg twice daily as tolerated. Of 26 patients evaluable for response, there were 3 partial responses per RECIST 1.1, and 6 partial responses and 1 complete response by modified RECIST. However, the median progression-free survival and overall survival of 3.6 and 7.1 months was disappointing. The most frequent axitinib-related grade 3/4 AEs were hypertension, thrombocytopenia, and diarrhea.

Chan et al. conducted a single-arm phase II trial in patients with inoperable HCC who underwent transarterial chemoembolization followed by maintenance axitinib 5 mg twice daily. The primary endpoint was the 2-year overall survival rate. In the intention-to-treat population (50 patients), the 2-year survival rate was 43.7%, which failed to meet the prespecified hypothesis of a 2-year survival rate of 50%. Grade 3 or greater axitinib-related complications included hand-foot skin reaction (14%) and hypertension (24%).

Clinical experience of axitinib combined with immunotherapies in advanced HCC is limited to a single phase 1B trial (VEGF Liver 100) in which interim results were reported on 22 patients treated with avelumab 10 mg/kg every two weeks plus axitinib 5 mg orally twice daily.[17] The most common grade 3 treatment-related AEs were hypertension (50.0%) and hand-foot syndrome (22.7%) and no grade 4/5 toxicities were observed. Objective response rates were 13.6% (95% CI, 2.9%-34.9%) and 31.8% (95% CI, 13.9%-54.9%) by RECIST and mRECIST, respectively. OS data were immature at data cutoff. These preliminary findings demonstrate that axitinib combined with avelumab was safe, consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies.

Complete information for axitinib may be found in the axitinib Investigator's Brochure.

1.2.4 Avelumab: Overview

Avelumab is a human IgG1 antibody directed against PD-L1 which competitively blocks the interaction between PD-L1 and its receptors PD-1 and B7-1. This results in the loss of inhibitory signals within immune cells including T cells which in turn induces anti-tumor immunity. T-cell exhaustion is frequently observed in HCC and PD-L1 expression is associated with worse prognosis, providing a rationale for targeting PD-1/PD-L1 in liver cancers which has now been confirmed in several clinical studies.[18,19]

1.2.5 Avelumab: Non-clinical experience

Binding of PD-L1 to PD-1 and B7-1 receptors found on T cells and antigen presenting cells suppresses T cell cytotoxic activity, proliferation, and cytokine production. In syngeneic mouse tumor models, avelumab mediated blockade of PD-L1 activity resulted in decreased tumor growth.[20] Given that PD-1 is expressed by many immune cell types and PD-L1 expression is chiefly confined to tumor cells in the tumor microenvironment, it is anticipated that anti-PD-L1 therapies such as avelumab may also have fewer immune related toxicities. Unique to the mechanism of action of avelumab compared to other existing anti-PD-1/PD-L1 antibodies is its ability to induce antibody-dependent cellular cytotoxicity activity.[21] Toxicology studies in cynomolgus monkeys determined a starting dose of 1 mg/kg for avelumab dose-escalation in humans and this starting dose level was subsequently supported by preliminary pharmacokinetic data showing that this dose level produced serum concentrations associated with pharmacological activity.[22]

1.2.6 Avelumab: Clinical experience

The phase 1, open-label, dose-escalation trial of avelumab (JAVELIN Solid Tumor) investigated the safety, pharmacokinetics, biological activity, and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. The phase 1a dose escalation portion was conducted at the Center for Cancer Research of the National Cancer Institute which examined 53 patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors for which no standard therapy existed or standard therapy had failed.[22] A 3 + 3 multicohort escalation design was used to asses 4 dose levels with 4 patients at 1 mg/kg, 13 at 3 mg/kg, 15 at 10 mg/kg, and 21 at 20 mg/kg. Pharmacokinetic analysis (n=86) showed a dose-proportional exposure between doses of 3 mg/kg and 20 mg/kg and a half-life of 95–99 hours at the 10 mg/kg and 20 mg/kg doses. Target occupancy was greater than 90% at doses of 3 mg/kg and 10 mg/kg. Of 18 patients treated in the dose-limiting toxicity analysis set, no dose-limiting toxicities were noted at dose levels 1, 2, or 3, and one dose-limiting toxicity was reported at dose level 4 in a patient with metastatic thymoma. Grade 3–4 treatment-related AEs

occurred in nine (17%) patients. Potential immune-related AEs occurred in 5 (7%) patients which was not associated with increasing dose levels of avelumab. Four (8%) of 53 patients had a partial response and 30 (57%) of 53 additional patients had stable disease, which was durable in three patients with a duration of 40 weeks or more. Based on these results, avelumab 10 mg/kg every 2 weeks was chosen as the dose for subsequent development.

In the expansion phase of the JAVELIN Solid Tumor study and in phase 2 studies, avelumab was tested in multiple cancer types including bladder cancer, stomach cancer, head and neck cancer, mesothelioma, non-small cell lung cancer, ovarian cancer, and renal cancer, which have not demonstrated new safety signals. As of 2020, avelumab is currently approved for metastatic Merkel cell carcinoma, locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy, and in combination with axitinib for the first-line treatment of patients with advanced renal cell carcinoma.

The approval of avelumab for Merkel cell carcinoma was based on results from the phase II JAVELIN Merkel 200 study which enrolled 88 patients with refractory and metastatic Merkel cell carcinoma.[23] Avelumab was given intravenously at a dose of 10 mg/kg every 2 weeks and the primary endpoint was confirmed objective response according to RECIST 1.1. The proportion of patients who achieved an objective response was 28 (31.8%), including 8 complete responses and 20 partial responses. Five grade 3 treatment-related AEs occurred in four (5%) patients: lymphopenia in two patients, blood creatine phosphokinase increase in one patient, aminotransferase increase in one patient, and blood cholesterol increase in one patient. No treatment-related grade 4 AEs or treatment-related deaths were reported.

In a pooled analysis of two cohorts in the expansion phase of the JAVELIN Solid Tumor study, 329 patients with advanced or metastatic urothelial carcinoma that had progressed after at least one previous platinum-based chemotherapy received avelumab 10 mg/kg every 2 weeks.[24] The primary endpoint was confirmed best overall response and the overall response of complete or partial response was recorded in 27 patients (17%), including nine (6%) complete responses and 18 (11%) partial responses. The most frequent treatment-related AEs were infusion-related reaction (29%) and fatigue (16%). Grade 3 or worse treatment-related AEs occurred in 8% patients, the most common of which were fatigue (2%), and asthenia, elevated lipase, hypophosphataemia, and pneumonitis (1% each). 8% of 249 patients had a serious adverse event related to treatment with avelumab, and one treatment-related death occurred (pneumonitis).

In the open-label, dose-finding and dose-expansion, phase 1b JAVELIN Renal 100 trial, patients with advanced renal-cell carcinoma enrolled in the dose-finding phase received 5 mg axitinib orally twice daily for 7 days, followed by combination therapy with 10 mg/kg avelumab intravenously every 2 weeks and 5 mg axitinib orally twice daily.[24] Based on the pharmacokinetic data from the dose-finding phase, patients in the expansion phase directly received 10 mg/kg avelumab intravenously every 2 weeks and 5 mg axitinib orally twice daily. Six of six patients in the dose-finding phase and 26 of 49 patients in the dose-expansion phase had confirmed objective responses. 32 (58%) of 55 patients had grade 3 or worse treatment-related AEs, the most frequent being hypertension in 16 (29%) patients and increased concentrations of alanine aminotransferase, amylase, and lipase, and palmar-plantar erythrodysaesthesia syndrome in four (7%) patients each. These encouraging results led to the phase 3 JAVELIN Renal 101 study which randomly assigned patients in a 1:1 ratio to receive avelumab (10 mg/kg) intravenously every 2 weeks plus axitinib (5 mg) orally twice daily or sunitinib (50

mg) orally once daily for 4 weeks (6-week cycle).[25] The primary end points were progression-free survival and overall survival among patients with programmed death ligand 1 (PD-L1)-positive tumors. Among the 560 patients with PD-L1-positive tumors (63.2%), the median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib. In the overall population, the median progression-free survival was 13.8 months, as compared with 8.4 months. Among the patients with PD-L1-positive tumors, the objective response rate was 55.2% with avelumab plus axitinib and 25.5% with sunitinib. AEs of any grade during treatment occurred in 432 of 434 patients (99.5%) who received avelumab plus axitinib and in 436 of 439 patients (99.3%) who received sunitinib. AEs of grade 3 or higher during treatment occurred in 309 patients (71.2%) and 314 patients (71.5%) in the respective groups. The most frequent grade 3 or higher toxicities with avelumab plus axitinib was hypertension (25.6%), diarrhea (6.7%), and palmar-plantar erythrodysaesthesia syndrome (5.8%). AEs that occurred during treatment led to discontinuation of both avelumab and axitinib in 33 patients (7.6%) who received the combination and led to discontinuation of sunitinib in 59 patients (13.4%) who received sunitinib.

Complete information for avelumab may be found in the avelumab Investigator's Brochure.

1.2.7 Bavituximab: Overview

Bavituximab is a chimeric monoclonal antibody directed against the membrane phospholipid phosphatidylserine (PS). While phosphatidylserine is normally confined to the inner leaflet of the plasma membrane, phosphatidylserine is externalized during apoptosis, cell injury, cell activation and malignant transformation. Bavituximab exerts anti-tumor effects by targeting exposed phosphatidylserine in the tumor vascular endothelium which induces tumor vessel destruction and immune cell recruitment. Clinical studies have demonstrated that bavituximab is well-tolerated, and preliminary evidence suggests that bavituximab combined with immune checkpoint inhibitors has anti-tumor activity in HCC.

1.2.8 Bavituximab: Non-clinical experience

Phosphatidylserine is a highly immunosuppressive molecule typically expressed on the inner leaflet of the plasma membrane of normal cells but "flips" and becomes externalized to the outer leaflet of the plasma membrane on cells that line tumor blood vessels and tumor cells creating a specific target for anticancer treatments. Bavituximab is an engineered immunoglobulin gamma 1 (IgG1) chimeric (human/mouse) mAb containing the variable region sequences of the murine phosphatidylserine targeting mouse antibody 3G4(2aG4) and human IgG1 k constant region sequences that targets phosphatidylserine (PS) after binding to 2-glycoprotein 1 (2GP1). By targeting phosphatidylserine, bavituximab induces tumor-infiltrating lymphocytes and pro-inflammatory cytokines which is enhanced with anti-PD-1/PD-L1 therapy. In addition, bavituximab repolarizes myeloid derived suppressor cells and M2 macrophages to M1, resulting in dendritic cell maturation and induction of tumor-specific cytotoxic T-lymphocyte immunity.

Nonclinical experiments have shown that antibody-mediated phosphatidylserine targeting can override phosphatidylserine-mediated immunosuppression, reactivate innate tumor immunity, and evoke adaptive antitumor immunity. In genetically modified nonclinical murine tumor models, phosphatidylserine targeting induces potent tumor-specific T-cell immunity in the transgenic adenocarcinoma mouse prostate tumor model such that the combination of anti-PS with castration cured 35% of the animals, compared to none in control groups. In separate pre-clinical studies, the use of antibodies against PD-1 or PD-L1 have demonstrated

similar activity as single agents and when combined with other immune oncology agents.

To support clinical development, bavituximab was evaluated in a series of dose range finding, repeated dose and specialized IV toxicology studies in appropriate species and in vitro systems. In vivo toxicology studies consisted of non-GLP dose range finding studies in the Sprague-Dawley® (SD) rat, rabbit and cynomolgus monkey as single IV dose administration, followed by GLP 8-week once-weekly dosing toxicology studies in the rat and monkey. The reversibility of any observed toxicity was determined in recovery studies included as part of the protocol for selected studies. The in vivo studies employed intravenous bolus dosing of bavituximab according to the current clinical dosing regimen and route of administration. Toxicokinetic (TK) analyses were conducted in rats and monkeys to facilitate correlating observed toxicity to systemic exposure to bavituximab.

The nonclinical safety assessment program that has been undertaken fully supports the continual use of bavituximab in clinical trials in oncology patients. The nonclinical effects of bavituximab have been assessed in a comprehensive panel of studies, addressing the relationships of pharmacology, pharmacokinetics/ toxicokinetics, immunogenicity and toxicology; the target tissues for toxicity; the NOAELs and LOAELs; the noninvasive monitors for the key toxicologic responses; and the reversibility of adverse effects. Among the recovery animals at the high dose (100 mg/kg) in the rat toxicology study, there remained evidence of microscopic sub endocardial inflammation and/or fibrosis, however, there were no coagulation abnormalities. Similarly, bavituximab-related microscopic changes in monkeys were confined to a mild thrombus within the right ventricle of one male at 100 mg/kg and no coagulation abnormalities in the recovery phase. Results from the bavituximab nonclinical program to date indicate a therapeutic benefit of combining bavituximab with conventional (chemotherapy) or immunotherapy (checkpoint blockade) for continued clinical evaluations and support the safety of the proposed dose of 3 mg/kg bavituximab administered intravenously once weekly in patients.

1.2.9 Bavituximab: Clinical experience

To date, the clinical development program of bavituximab has enrolled approximately 900 patients, of whom over 600 patients have been treated with bavituximab. Most patients were treated with combination therapy in oncology studies. Common AEs (20%) were reported in patients receiving bavituximab, including the following: nausea, alopecia, fatigue, diarrhea, neutropenia, anemia, pyrexia, and asthenia. Many of the reported common AEs were considered to be related to the concomitant administration of chemotherapy or the patient's underlying malignancy.

Phase I and Ib single-agent studies of bavituximab in combination with chemotherapy have been completed in patients with advanced cancer. Based on efficacy results from these studies and on PK data (which determined the maximum binding of β2-GP1), a dose of 3 mg/kg bavituximab was determined and selected for further clinical study. The studies also showed the tolerability profile to be consistent with expectations based on animal studies and demonstrated adequate efficacy to warrant further study. Several Phase II studies of bavituximab in combination with chemotherapy have been completed.

The double-blind, placebo-controlled, multicenter, phase 3 SUNRISE study tested the efficacy and safety of bavituximab combined with docetaxel in patients with previously treated advanced non-squamous lung adenocarcinoma.[26] Patients were randomized 1:1 to receive docetaxel 75 mg/m^2 intravenously on day 1 of a

21-day cycle plus blinded study treatment (either placebo or bavituximab 3 mg/kg intravenously weekly). The primary end point was overall survival and secondary end points included progression-free survival, objective response rate, and safety. 597 patients were enrolled and the median overall survival was 10.5 months in the docetaxel plus bavituximab arm and 10.9 months in the docetaxel plus placebo arm. There was also no difference in progression-free survival (HR 1.00; 95% CI 0.82–1.22; P = 0.990) or objective response rates (14% in the docetaxel plus bavituximab arm and 11% in the docetaxel plus placebo arm; P = 0.18). In a post hoc analysis, overall survival favored the bavituximab arm among patients who received immune checkpoint inhibitor therapy after study therapy (n = 93, 16%) with a median survival time not reached versus 12.6 months (HR 0.46; 95% CI 0.26–0.81; P = 0.006). There was no apparent difference in rates of characteristic immune-related adverse events, and AEs in both arms were largely consistent with AEs expected with docetaxel monotherapy. While this study did not support the addition of bavituximab to chemotherapy in refractory lung adenocarcinoma, the improved overall survival of patients who received bavituximab and subsequent immunotherapy rather than targeted therapies or chemotherapy suggests that bavituximab may sensitize cancers to immune checkpoint inhibitors.

Bavituximab plus sorafenib was examined in a single-arm phase 2 trial of patients with unresectable HCC, Eastern Cooperative Oncology Group (ECOG) score ≤ 2, and Child-Pugh score A/B7.[27] Time to progression was the primary endpoint and 38 patients received intravenous bavituximab 3 mg/kg weekly and oral sorafenib 400 mg twice daily. The median time to progression of patients receiving bavituximab and sorafenib was 6.7 months, which did not reach pre-specified significance. Treatment-related AEs were observed in 63% of patients, with the most commonly reported therapy-related symptoms being diarrhea (32%), fatigue (26%), and anorexia (24%). There were no grade 4-5 AEs and grade 3 AEs included diarrhea (5%), vomiting (3%), upper gastrointestinal bleeding (3%), fatigue (3%), hypertension (3%), and palmar-plantar erythrodysaesthesia syndrome (3%). These AEs were consistent with toxicities expected with monotherapy sorafenib. While this study did not provide evidence for improved efficacy of bavituximab plus sorafenib over sorafenib alone, the combination regimen was well-tolerated and safe in patients with advanced HCC and underlying liver disease.[27]

Bavituximab in combination with the anti-PD-1 antibody pembrolizumab is now under investigation across 3 disease types including gastroesophageal cancers (NCT04099641), head and neck cancers (NCT04150900), and HCC (NCT03519997). A single-arm phase 2 study with a two-stage design for patients with unresectable HCC is currently being conducted at the Harold C. Simmons Comprehensive Cancer Center and Parkland Hospital and Health System. Patients receive pembrolizumab 200 mg intravenously every 3 weeks and bavituximab 3 mg/kg intravenously weekly. The primary endpoint is the best objective response rate. This study is currently enrolling in its second stage after meeting its predefined response rate to continue enrollment. Preliminary analysis of 36 patients who received at least one infusion of pembrolizumab and bavituximab and evaluable for safety shows that this combination is safe and well tolerated in patients with advanced HCC with no unexpected safety events. Treatment-related AEs are shown below:

Treatment-related adverse event	All grade (%)	Grade 3 or 4 (%)
Colitis/diarrhea	7 (19.4)	2 (5.6)
Aspartate aminotransferase increased	5 (13.9)	0
Alanine aminotransferase increased	4 (11.1)	0

Maculopapular rash	4 (11.1)	1 (2.8)
Chills	3 (8.3)	0
Pruritus	3 (8.3)	0
Arthralgia	2 (5.6)	0
Fatigue	2 (5.6)	0
Thrombocytopenia	2 (5.6)	0
Abdominal pain	1 (2.8)	0
Creatinine increased	1 (2.8)	0
Dyspnea	1 (2.8)	0
Fever	1 (2.8)	0
Mucositis	1 (2.8)	0
Albumin decreased	1 (2.8)	0

1.3 Rationale

Sensitizing HCC to immunotherapy using axitinib. Preclinical evidence indicates that VEGF and VEGF-dependent angiogenesis may induce immune suppression in tumors by impairing antigen presenting cells and effector T-cells, and enhancing T-regulatory cells and monocytes.[28] Disruption of the endothelium may also enhance lymphocyte recruitment within tumors.[29,30] Thus, targeting VEGF may reprogram the tumor immune microenvironment to render cancers more vulnerable to immunotherapies. Indeed, the use of anti-VEGF strategies as an immunotherapy adjuvant has been associated with clinical benefit in multiple cancer types including HCC, and no new safety signals.[8,31-33] While the clinical benefit of monotherapy axitinib in HCC is modest, use of axitinib as an immunotherapy adjuvant may circumvent primary resistance mechanisms to immune checkpoint inhibitors in HCC leading to more frequent or robust anti-tumor immunity. This is consistent with results from the phase 3 IMbrave150 study which demonstrated the superiority of atezolizumab plus bevacizumab versus sorafenib alone.[8]

Rationale for combining axitinib and immune checkpoint inhibitor with the anti-phosphatidylserine antibody bavituximab. Phosphatidylserine is a cytoplasmic-facing anionic phospholipid which has multiple essential functions in cellular membranes.[34,35] Externalization of phosphatidylserine occurs as a result of apoptosis or cellular stress, but is also frequently observed in cancer cells and within stromal cells.[34] Of therapeutic relevance, exposed phosphatidylserine and phosphatidylserine-dependent receptors including the Tyro3, Axl, and Mer (TAM) family of negative immune regulators facilitate cancer immune escape.[34] Indeed, preclinical evidence indicates that antibody-based targeting of phosphatidylserine promotes pro-inflammatory pathways, recruitment of tumoricidal macrophages, dendritic cell maturation, and potent T-cell immunity in multiple cancer models.[36] While bavituximab has been demonstrated to be well tolerated as a single agent and in combination with chemotherapy, its use as a single agent in a phase I study of refractory advanced solid cancers and in combination with docetaxel in advanced non-small-cell lung cancer did not show significant clinical benefit.[26,37,38] Notably, prior use of bavituximab was not guided by its immunogenic mechanism of action. The pleiotropic pro-inflammatory and -immunogenic effects of bavituximab on tumor cells, immune cells, and stroma suggests that it may enhance the activity of immune checkpoint inhibitors. This is supported by preclinical evidence that targeting phosphatidylserine enhances either PD-1 or CTLA-4 blockade in melanoma, breast, and colon cancer models, and preliminary results from a phase II study underway at UT Southwestern testing the combination of bavituximab and pembrolizumab in HCC.[39-41] Initial results from a two-stage phase II study testing bavituximab plus pembrolizumab in advanced HCC has demonstrated good tolerability and promising activity based on objective response rates meeting pre-specified goals in order to transition to the second stage of the study. Given the complimentary

immune augmenting mechanisms of targeting VEGF and phosphatidylserine, we hypothesize that combination axitinib, bavituximab, and avelumab, a PD-L1 antibody, represents a novel and rational immunotherapy regimen in HCC. We propose to test this by studying the clinical efficacy and safety of combination axitinib, bavituximab, and avelumab treatment in a single arm phase II trial using a two-stage design.

1.4 Rationale for Treatment Beyond Progression

Across cancer types, immune checkpoint inhibitors have been shown to induce complete response, partial response, and stable disease after initial evidence of radiographic increase in tumor burden. This initial increase in tumor burden may be attributed to immune-cell infiltration in the setting of a T-cell response. Therefore, this study will allow all patients to continue their assigned treatment after apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favorable by the investigator. Treatment beyond progression should be considered when the patient is stable (or improving) symptomatically and if tumor reassessment can be performed within a short period.

1.5 Correlative Studies

Molecular profiling including exome and transcriptome sequencing of baseline or multiplex immunohistochemistry of archived tissue specimens will allow us to identify predictive markers of treatment response. As this testing will be performed on tissue obtained as a component of routine care, there is no additional risk to the patient. Tissue sampling at the time of progression is encouraged but not required. Tissue at progression may undergo similar testing to identify markers or mechanisms of resistance.

Archival tissue will also be examined using the XernaTM TME Panel which is a RNA-based gene expression assay to classify patients based on the biology of the tumor microenvironment (TME).

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the best objective response rate assessed by RECIST guidelines (version 1.1) of combination axitinib, bavituximab, and avelumab in patients with advanced HCC not previously treated with systemic therapies.

2.2 Secondary Objectives

2.2.1 To determine the disease control rate, overall survival, 6-month progression-free survival, and duration of response of combination axitinib, bavituximab, and avelumab compared to historical controls.

2.2.2 To evaluate the overall safety profile of combination axitinib, bavituximab, and avelumab.

2.3 Exploratory Objectives

2.3.1 To explore the objective response rate as assessed by iRECIST of combination axitinib, bavituximab, and avelumab in patients with advanced HCC.

2.3.2 To explore the utility of tissue and/or serum-based markers as predictors of therapy response.

2.4 Endpoints

Primary endpoint:
Objective response rate (ORR) based on Investigator assessment per RECIST v.1.1.

Secondary endpoint:
Progression-free survival (PFS), overall survival (OS), and duration of response (DR) based on Investigator assessment, per RECIST v.1.1.

Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Patient must have a histologically confirmed diagnosis consistent with HCC; known fibrolamellar HCC, or combined HCC-cholangiocarcinoma will be excluded.

3.1.2 Locally advanced or metastatic disease

3.1.2.1 Patients with locally advanced or metastatic disease must have disease deemed not amenable to surgical and/or locoregional therapies or patients who have progressed following surgical and/or locoregional therapies.

3.1.2.2 Measurable disease, as defined as lesions that can accurately be measured in at least one dimension according to RECIST version 1.1 at least 1 cm with contrast enhanced dynamic imaging (magnetic resonance imaging or computed tomography).

3.1.3 Availability of recent formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or slides (biopsied tumor lesion should not be a RECIST target lesion): 1) the biopsy or resection was performed within 2 years of AND 2) the patient has not received any intervening systemic anti-cancer treatment from the time the tissue was obtained.

3.1.4 Prior therapy is allowed provided the following are met: at least 4 weeks since prior locoregional therapy including surgical resection, chemoembolization, definitive radiotherapy with intent of disease control, or ablation. Provided target lesion has increased in size by 25% or more or the target lesion was not treated with locoregional therapy. Patients treated with palliative radiotherapy for symptoms will be eligible as long as the target lesion is not the treated lesion and radiotherapy will be completed at least 2 weeks prior to study drug administration.

3.1.5 Age ≥ 18 years

3.1.6 Child-Pugh Score A

3.1.7 ECOG Performance score of 0-1

3.1.8 Adequate organ and marrow function as defined below:

3.1.8.1 Platelet count ≥ 50,000/mm^3

3.1.8.2 Hgb ≥ 8.5 g/dl

3.1.8.3 Absolute neutrophil ≥ 1,500 cells/mm^3

3.1.8.4 Total bilirubin ≤ 2.0 mg/ml

3.1.8.5 INR ≤ 1.7

3.1.8.6 AST, ALT ≤5 times ULN

3.1.8.7 Serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min

3.1.8.8 Albumin ≥ 2.5 g/dl

3.1.9 All men, as well as women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) 4 weeks prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9.1 A female of child-bearing potential is any woman (regardless of sexual orientation, marital status, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.10 Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication.

3.1.11 Subjects are eligible to enroll if they have non-viral-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:

1) HBV-HCC: Controlled (treated) hepatitis B subjects will be allowed if they meet the following criteria: Antiviral therapy for HBV must be given for at least 12 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Subjects on active HBV therapy with viral loads under 100 IU/ml should stay on the same therapy throughout study treatment. Subjects who are anti-HBc (+), negative for HBsAg, negative for anti-HBs, and have an HBV viral load under 100 IU/mL do not require HBV anti-viral prophylaxis.

2) HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody. Patients who have failed HCV therapy as evidenced by detectable HCV RNA will be eligible. Subjects with chronic infection by HCV who are treated (successfully or treatment failure) or untreated are allowed on study. In addition, subjects with successful HCV treatment are allowed as long as there are ≥4 weeks between completion of HCV therapy and start of study drug. Successful HCV treatment definition: SVR12.

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

3.1.13 Patients who have received the vector, protein subunit, or nucleic acid COVID-19 vaccines are eligible to enroll.

3.2 Exclusion Criteria

3.2.1 Prior liver transplant.

3.2.2 Prior systemic therapy directed at advanced or metastatic HCC.

3.2.3 Prior immunotherapy with IL-2, or anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

3.2.4 Prior therapy with axitinib or any prior therapies with other VEGF pathway inhibitors.

3.2.5 Clinically significant, uncontrolled heart disease and/or recent events including any of the following:

3.2.5.1 History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 12 months prior to screening).

3.2.5.2 History of documented congestive heart failure (New York Heart Association functional classification III-IV).

3.2.5.3 History of cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within 6 months of screening.

3.2.5.4 Patient has a left ventricular ejection fraction <40% as determined by MUGA scan or ECHO (MUGA and ECHO are not required prior to enrollment).

3.2.6 Known human immunodeficiency virus (HIV) positive (testing not required).

3.2.7 History of cerebrovascular accident, transient ischemic attack, or thromboembolic events (including both pulmonary embolism and deep venous thrombus but not including tumor thrombus) within the last 6 months.

3.2.8 Hypersensitivity to IV contrast; not suitable for pre-medication.

3.2.9 Active or fungal infections requiring systemic treatment within 7 days prior to screening.

3.2.10 Known history of, or any evidence of, interstitial lung disease or active noninfectious pneumonitis.

3.2.11 Evidence of poorly controlled hypertension which is defined as systolic blood pressure >159 mmHg or diastolic pressure >99 mmHg despite optimal medical management.

3.2.12 Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.

3.2.13 Active, known, or suspected autoimmune disease with the exception of subjects with vitiligo, type I diabetes mellitus, resolved childhood asthma or atopy. Subjects with suspected autoimmune thyroid disorders may be enrolled if they are currently euthyroid or with residual hypothyroidism requiring only hormone replacement. Subjects with psoriasis requiring systemic therapy must be excluded from enrollment.

3.2.14 Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the study or compromise compliance with the protocol (e.g. chronic pancreatitis, active untreated or uncontrolled fungal, bacterial, or viral infections, etc.).

3.2.15 Known history of active bacillus tuberculosis.

3.2.16 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of study administration. Inhaled or topical steroids and adrenal replacement doses >10 mg/day prednisone equivalents are permitted in the absence of autoimmune disease.

3.2.17 Patient who has received definitive radiotherapy with the sole intent of disease control ≤ 4 weeks prior to study entry. Palliative radiotherapy for symptomatic control (such as to bone metastases) is acceptable (if completed at least 2 weeks prior to study drug administration and no additional radiotherapy for the same lesion is planned).

3.2.18 Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).

3.2.19 Clinically apparent ascites on physical examination, ascites present on imaging studies is allowed.

3.2.20 Known severe hypersensitivity reactions to monoclonal antibodies (Grade 3).

3.2.21 Active gastrointestinal bleeding within previous 2 months.

3.2.22 History of any condition requiring anti-platelet therapy (aspirin >300 mg/day, clopidogrel >75 mg/day).

3.2.23 Diagnosis of any other malignancy within 5 years prior to screening visit, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation, or castration).

3.2.24 Prisoners or subjects who are involuntarily incarcerated.

3.2.25 History of leptomeningeal disease.

3.2.26 Symptomatic or clinically active brain metastases.

3.2.27 Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after contraception and until the termination of gestation, confirmed by a positive hCG laboratory test.

3.2.28 Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab(+) and detectable HCV RNA) at study entry.

3.2.29 Known prior or suspected hypersensitivity to study drugs or any component in their formulations.

3.2.30 Current use or anticipated need for drugs that are known strong CYP3A4/5 inducers, including their administration within 10 days prior to patient receiving the first study treatment, eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St John's wort.

3.2.31 Patients with 2+ proteinuria on urine dipstick analysis and confirmed to have ≥2 grams of protein in a 24-hour urine collection.

3.2.32 Current use or anticipated need for treatment with drugs or foods that are known strong CYP3A4/5 inhibitors, including their administration within 10 days prior to patient receiving the first study treatment, (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits, ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 For the purpose of this study, the investigational products are avelumab, axitinib, and bavituximab. All investigational drugs will be administered on an outpatient basis.

4.1.2 Avelumab dosage form and packaging: Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20.0 mg/mL solution and will be supplied by Pfizer in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal. Avelumab will be dosed at the investigational site. For application in this trial, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection).

4.1.3 Avelumab administration: Avelumab will be administered as a 1-hour IV infusion on Day 1 and Day 15 of each 28-day cycle. Avelumab may be administered up to 3 days before or after the scheduled Day 1 of each dose due to administrative reasons. Avelumab should be administered at least 30 minutes after the bavituximab infusion (on days when both are administered). In order to mitigate infusion-related reactions, a required premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen will be administered immediately prior to administration of avelumab for the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Sites should make every effort to target infusion timing to be as close to 1 hour as possible (no longer than 2 hours).

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 7 days prior to dosing for every cycle. If the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the prior dose, the amount of study drug required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. The maximum dose is 2000 mg for all adult patients. Avelumab dose reduction for toxicity management is not permitted, however next cycle administration may be omitted due to persisting toxicity.

4.1.4 Axitinib dosage form and packaging: Axitinib will be supplied by Pfizer as 1 mg and 5 mg film-coated tablets for oral administration in light-resistant high-density polyethylene (HDPE) bottles with desiccant.

4.1.5 Axitinib administration: Axitinib will be provided in quantities appropriate for the study visit schedule. A qualified staff member will provide the study treatment via a unique container number. Axitinib will be dispensed every 4 weeks or as otherwise indicated.

Axitinib will be administered orally BID at approximately the same time in the morning and evening on a continuous dosing schedule. Axitinib tablets are to be taken approximately 12 hours apart and may be administered without regard to meals or avelumab and bavituximab administration. Tablets must not be crushed, split, or dissolved, and patients should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing.

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

4.1.6 Bavituximab dosage form and packaging: Bavituximab is supplied OncXerna as a sterile, preservative-free solution with 10 mM acetate at pH 5.0 and diluted with 0.9% saline (normal saline) to a final volume of 100 mL.

4.1.7 Bavituximab administration: Bavituximab will be administered weekly on Days 1, 8, 15 and 22 of the 28-day cycle.
Infusion preparation and administration are to be performed as follows:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used). Fill treatment into a sterile glass bottle or plastic IV bag.
2. Using aseptic techniques, repeat procedure until the calculated volume has been put into the container. Bring the final volume to 100 mL using 0.9% Sodium Chloride Injection, USP.
3. Administer through a low protein binding 0.2-micrometer in-line filter (placed as proximal to the patient as practical).
4. Affix the infusion line and prime it with infusate before starting the infusion. Infuse the solution intravenously over 90 (± 10) minutes. No reduction in infusion time will be permitted. Flush the line with normal saline after infusion.

REGIMEN DESCRIPTION

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Bavituximab		3 mg/kg in NS	IV over 90 min	Days 1, 8, 15, 22	4 weeks (28 days)
Avelumab	Premedicate with diphenhydramine and acetaminophen prior to avelumab.	10 mg/kg in NS (maximum dose is 2000 mg)	IV over 60 min at least 30 min **after** bavituximab	Days 1, 15	
Axitinib		5 mg tablet	PO BID	Daily	

4.2 Safety Lead-in, Toxicities, and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Section 5.3). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.

4.2.1 Safety Lead-in and Dose-limiting Toxicities

A safety and tolerability assessment will be performed for patients treated with axitinib, bavituximab, and avelumab after the first 6 patients evaluable for dose-limiting toxicities have completed 1 cycle (ie, Cycle 1 Day 28). Patients will be considered evaluable for dose-limiting toxicities assessment if they have completed all scheduled study visits during the first cycle and have received 2 (100%) of the 2 planned doses of avelumab and at least 3 (75%) of the 4 planned doses of bavituximab in Cycle 1.

Dose-limiting toxicities are defined as any Grade 3 or greater AE that occurs during the first cycle (28 days) and are considered to be related (possible, probable, or definite) to study drug, specifying attribution to axitinib, avelumab, bavituximab, or all drugs. Intolerable Grade 2 gastrointestinal toxicities (such as persistent nausea/vomiting or diarrhea) will also be considered dose-limiting toxicities if they are considered to be related to any study drug. See Tables 2 and 3 below and Section 7.0 for AEs associated with axitinib, avelumab, or bavituximab.

Enrollment of additional patients after the first 6 potentially evaluable patients for dose limiting toxicities will be suspended until after assessment of the safety lead-in phase by the UTSW Simmons Cancer Center Gastrointestinal Disease-Oriented Teams (GI DOT) is complete.

- If ≤1 dose-limiting toxicity occurs, trial enrollment will proceed without any modifications.
- If ≥2 dose-limiting toxicities occurs, all treatment-related AEs will be reviewed by the GI DOT for consideration of modification or termination of the study. Modifications may include reducing the starting dose of axitinib by one dose level to 3 mg BID for all subsequent patients enrolled and not permitting dose re-escalation above dose level 0.

4.2.2 Axitinib dose reduction and re-escalation

Dosing interruption and/or dose reduction by 1, and if needed, 2 dose levels (one dose level decrease at a time) as indicated in Table 1 will be allowed depending on the type and severity of toxicity encountered. Patients who have undergone dose reduction may undergo dose re-escalation to prior dose levels in the absence of grade 2 or greater AEs for at least 28 days.

If patient develops decompensated cirrhosis (Child Pugh B), axitinib dosing should be reduced to the -1 dose level. Subsequent dosing can be increased or decreased according to the patient's tolerance. Patients must not have irreversible toxicities related to the axitinib to be eligible for dose re-escalation of axitinib after dose reduction.

Table 1. Axitinib dose levels.

Dose level	Dose
0	5 mg BID
-1	3 mg BID
-2	2 mg BID

Further dose reductions less than dose level -2 are not permitted.

4.2.3 Axitinib dose modifications, and avelumab and bavituximab infusion omissions for treatment-related toxicities.

Toxicities related to axitinib may primarily stem from the known on-target effects of inhibiting VEGFR including hypertension and proteinuria. In contrast, toxicities related to avelumab and bavituximab may be due to immune related AEs (irAEs). Management of specific irAEs should be consistent with American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (2018). For Grade 2 irAEs, avelumab and bavituximab should be permanently discontinued if AE does not resolve to at least Grade 1 within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. Specific dose modifications and infusion omissions depend on the severity of toxicities as detailed in Table 2 and Table 3.

If any study drug is withheld or discontinued, the remaining study drugs can be continued as long as the patient is experiencing clinical benefit, as determined by the investigator per medical judgment.

Table 2. Dose modifications and infusion omissions for toxicities.

Toxicity	NCI CTCAE Grade	Axitinib	Avelumab	Bavituximab
Hypertension	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	If not on maximal anti-hypertensive treatment, institute new or additional antihypertensive medication and continue at the same dose level. If on maximal anti-hypertensive treatment, reduce by 1 dose level.	Continue as per schedule.	Continue as per schedule.
	3	For first and subsequent occurrence, withhold until BP is less than 150/100 mm Hg and adjust antihypertensive medication. Then, reduce by 1 dose level and resume treatment.	Continue as per schedule.	Continue as per schedule.

		If on maximal anti-hypertensive treatment, reduce by 1 dose level. If axitinib dosing is interrupted, patients receiving antihypertensive medications should be monitored closely for hypotension as BP usually decreases within 1-2 days after the last dose.		
	4	Repeat dose reduction by one lower dose level. Permanent discontinuation if already on maximal anti-hypertensive treatment.	Continue as per schedule.	Continue as per schedule.
Proteinuria	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2-3	Continue at same dose level if proteinuria is <2gm/24 hours. If proteinuria is >2gm/24 hours, withhold until proteinuria is <2 g/24 hours. Time of repeat urine collection is at investigator discretion. Then, resume at the same dose level or reduce by 1 dose level as per investigator judgment.	Continue as per schedule.	Continue as per schedule.
irAEs (except for endocrinopathies)	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	Continue at same dose level.	Withhold until Grade ≤1. If Grade 2 event does not resolve to Grade 1 after holding for at least 2 cycles (8 weeks), permanently discontinue.	Withhold until Grade ≤1. If Grade 2 event does not resolve to Grade 1 after holding for at least 2 cycles (8 weeks), permanently discontinue.
	3-4	Hold treatment until Grade ≤1 and restart at same dose level.	Permanently discontinue.	Permanently discontinue.
Immune related hypothyroidism	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	Continue at same dose level.	May hold until patient is on thyroid hormone supplementation or symptoms resolve to baseline.	May hold until patient is on thyroid hormone supplementation or symptoms resolve to baseline.

	3-4	Hold treatment until Grade ≤1 and restart at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1 while on thyroid supplementation. Patient should be referred to Endocrine.	Hold until symptoms resolve to baseline or until Grade ≤1 while on thyroid supplementation. Patient should be referred to Endocrine.
Immune related hyperthyroidism	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	Continue at same dose level.	May hold until patient symptoms resolve to baseline. Consider β - blockers for symptomatic control rather than steroids initially. For persistent symptoms >6 weeks, patient will need to be evaluated for Grave's disease.	May hold until patient symptoms resolve to baseline. Consider β - blockers for symptomatic control rather than steroids initially. For persistent symptoms >6 weeks, patient will need to be evaluated for Grave's disease.
	3-4	Hold treatment until Grade ≤1 and restart at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1 with appropriate therapy. Patient should be referred to Endocrine.	Hold until symptoms resolve to baseline or until Grade ≤1 with appropriate therapy. Patient should be referred to Endocrine.
Immune related adrenal insufficiency	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	Continue at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1 with replacement hormones. Maintenance replacement therapy with prednisone 5-10 mg daily (or equivalent). May require fludrocortisone (0.1 mg/d) for mineralcorticoid replacement. May need to use doses 2-3 times maintenance dose for management of acute symptoms.	Hold until symptoms resolve to baseline or until Grade ≤1 with replacement hormones. Maintenance replacement therapy with prednisone 5-10 mg daily (or equivalent). May require fludrocortisone (0.1 mg/d) for mineralcorticoid replacement. May need to use doses 2-3 times maintenance dose for management of acute symptoms.
	3-4	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Immune related hypophysitis	1	Continue at same dose level.	Consider holding until patient is stabilized on replacement therapy. Patient should be referred to Endocrine.	Consider holding until patient is stabilized on replacement therapy. Patient should be referred to Endocrine.
	2	Continue at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1 with replacement hormones. Patient should be referred to Endocrine.	Hold until symptoms resolve to baseline or until Grade ≤1 with replacement hormones. Patient should be referred to Endocrine.

	3-4	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Immune related diabetes	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	Continue at same dose level.	Considering holding until patient is stabilized (Grade ≤1) on replacement therapy. Insulin should be initiated as default treatment rather than oral therapies. Patient should be referred to Endocrine.	Considering holding until patient is stabilized (Grade ≤1) on replacement therapy. Insulin should be initiated as default treatment rather than oral therapies. Patient should be referred to Endocrine.
	3-4	Hold treatment until Grade ≤1 and restart at same dose level.	Hold until patient is stabilized (Grade ≤1) on replacement therapy. Insulin should be initiated as default treatment rather than oral therapies. Patient should be referred to Endocrine.	Hold until patient is stabilized (Grade ≤1) on replacement therapy. Insulin should be initiated as default treatment rather than oral therapies. Patient should be referred to Endocrine.
Immune related colitis/diarrhea	1	Continue at same dose level.	Consider holding until symptoms resolve to baseline or until Grade ≤1. Consider antidiarrheals if other causes are excluded.	Consider holding until symptoms resolve to baseline or until Grade ≤1. Consider antidiarrheals if other causes are excluded.
	2	Continue at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1. Steroids may be considered if indicated on an individual basis.	Hold until symptoms resolve to baseline or until Grade ≤1. Steroids may be considered if indicated on an individual basis.
	3	Hold treatment until Grade ≤1 and restart at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1. Administer steroids at 1-2 mg/kg/d prednisone or equivalent with taper over 4 weeks. Patient should be referred to Gastroenterology. Consider colonoscopy.	Hold until symptoms resolve to baseline or until Grade ≤1. Administer steroids at 1-2 mg/kg/d prednisone or equivalent with taper over 4 weeks. Patient should be referred to Gastroenterology. Consider colonoscopy.
	4	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Immune related pneumonitis	1	Continue at same dose level.	Hold if there is progression with repeat CT chest at 3-4 weeks and treat as Grade 2.	Hold if there is progression with repeat CT chest at 3-4 weeks and treat as Grade 2.
	2	Continue at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1. Administer steroids at 1-	Hold until symptoms resolve to baseline or until Grade ≤1. Administer steroids at 1-

			2 mg/kg/d prednisone or equivalent with taper over 4 weeks. Consider Pulmonology consult. Monitor every 3-4 days, if no clinical improvement, treat as Grade 3.	2 mg/kg/d prednisone or equivalent with taper over 4 weeks. Consider Pulmonology consult. Monitor every 3-4 days, if no clinical improvement, treat as Grade 3.
	3-4	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Immune related hepatitis	1	Continue at same dose level.	Continue as per schedule.	Continue as per schedule.
	2	Continue at same dose level.	Hold until symptoms resolve to baseline or until Grade ≤1. Steroids may be considered if indicated on an individual basis.	Hold until symptoms resolve to baseline or until Grade ≤1. Steroids may be considered if indicated on an individual basis.
	3-4	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.

Table 3. Dose modifications for drug-related adverse events potentially associated with axitinib and not considered immune-related.

Toxicity	**NCI CTCAE Grade**	**Axitinib**
Diarrhea	1-2	Continue at same dose level.
	3	Hold until symptoms resolve to baseline or until Grade ≤1. Then, resume at the same dose level or reduce by 1 dose level as per investigator judgment.
	4	Permanently discontinue.
Hemorrhage/bleeding	1	For CNS bleeding, permanently discontinue. For non-CNS bleeding, continue at same dose level.
	2	For pulmonary and GI bleed (other than hemorrhoidal bleeding or in setting of colitis), permanently discontinue. For other bleeding events, hold until symptoms resolve to baseline or until Grade ≤1. Then, resume at the same dose level or reduce by 1 dose level as per investigator judgment.
	3-4	Permanently discontinue.
Palmar-plantar erythrodysesthesia syndrome	1-2	Continue at same dose level. Consider the use of topical pain relievers and/or moisturizing exfoliant creams.
	3	Hold until symptoms resolve to baseline or until Grade ≤1. Consider the use of topical or parenteral pain relievers and/or moisturizing exfoliant creams. Then, resume at the same dose level or reduce by 1 dose level as per investigator judgment.
AST, ALT or bilirubin elevation	1	Continue at same dose level.
	2	Hold until symptoms resolve to baseline or until Grade ≤1. Then, resume at same dose level.
	3-4	Hold until symptoms resolve to baseline or until Grade ≤1. Then, reduce by 1 dose level.
Hematologic abnormalities	1-3	Continue at same dose level.

	4	Hold until symptoms resolve to baseline or until Grade ≤1. Restart axitinib dose reduced by 1 dose level. Note: Grade 4 lymphopenia not associated with clinical events, (e.g, opportunistic infection) may continue on with axitinib.
Stevens-Johnson syndrome	3-4	Permanently discontinue.
Other non-hematologic toxicities and laboratory abnormalities	1-2	Continue at same dose level.
	3	Hold until symptoms resolve to baseline or until Grade ≤2. For toxicities controlled with symptomatic medications or asymptomatic laboratory abnormalities, continue at the same dose level or reduce by 1 dose level as per investigator judgment. For all other toxicities, reduce by 1 dose level.
	4	Hold until symptoms resolve to baseline or until Grade ≤2. Then, reduce by 1 dose level as per investigator judgment. Permanently discontinue axitinib for Grade 4 toxicities that meet any of the following conditions: 1) recurrent 2) life-threatening 3) reversible posterior leukoencephalopathy syndrome 4) arterial thrombosis/ischemia

4.2.4 Infusion related reactions.

Because avelumab and bavituximab are administered as infusions, infusion reactions are possible and may include symptoms such as fever, chills, shortness of breath, headache, and rigors. Infusion modifications depend on the severity of reactions as detailed in Table 4 below.

Table 4. Infusion-related reactions caused by avelumab or bavituximab.

NCI CTCAE Grade	Infusion modifications
1	Decrease the avelumab and/or bavituximab infusion rate by 50%.
2	Temporarily discontinue avelumab and/or bavituximab 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.
3-4	Stop the infusion immediately and disconnect infusion tubing from the patient. Patients may not receive further treatment.

4.3 Concomitant Medications/Treatments

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for administration of the inactivated influenza vaccine and protein subunit, vector, or nucleic acid COVID-19 vaccines.

4.3.1 Inhibitors and inducers of CYP enzymes

In vitro studies with human liver microsomes and recombinant CYP enzymes indicate that axitinib metabolism is primarily mediated by the CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

The concomitant use of strong CYP3A4/5 inhibitors (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits, ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan) are not permitted. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Consider a dose reduction (by approximately 50%) if axitinib must be dosed with a CYP3A4/5 inhibitor. If axitinib dose is reduced due to concomitant CYP3A4/5 inhibitor use, axitinib dose may be increased based on tolerability. Reference Section 4.2.1-Axitinib dose reduction and re-escalation, Table 1.

4.3.2 Prohibited concomitant medications

1) Antineoplastic systemic chemotherapy or biological therapy;
2) Immunotherapy not specified in this protocol;
3) Chemotherapy not specified in this protocol;
4) Investigational agents other than axitinib, avelumab, and bavituximab;

4.3.3 Concomitant surgery

If a major surgery or an interventional procedure is required, treatment with axitinib must be interrupted at least 24 hours before the procedure, and the patient's blood pressure should be monitored closely for hypotension. Patients may resume axitinib 7 days after minor surgery and 2-3 weeks after major surgery, assuming the wound has completely healed and there are no wound-healing complications. For surgical procedures, avelumab and bavituximab may be delayed as determined by the investigator. Reference Section 11.5 for both planned and emergency deviation reporting/approval requirements.

4.3.4 Concomitant radiation

Local radiotherapy (limited field) of isolated lesions with palliative intent is acceptable and allowed throughout the study if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should also be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered as a sign of disease progression. Lesions that have been radiated cannot be target lesions.

4.3.5 Steroid use

Given concerns that systemic steroids may impact the efficacy of immune checkpoint inhibitors, steroid use during treatment should be avoided. Steroid use is permitted as follows:

1) Therapeutic use for the management of irAEs.
2) Steroid replacement for adrenal insufficiency with maintenance doses ≤10 mg of prednisone daily.
3) Prophylactic use for contrast allergies prior to CT or MRI scans.

4.4 Registration Procedures

All subjects must be registered with the GI DOT before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the GI DOT clinical research manager. To register a subject, call 214-648-7031 Monday through Friday, 9:00AM-5:00PM.

UTSW will be given site number 01, and the satellite site will be 02. New subjects at UTSW will receive a number beginning with 01-001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc. The first subject consented at the satellite site will be 02-001.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 at UTSW will become 01-001-01 upon enrollment. If subject 01-002 screen fails, and subject 02-001 is the next subject enrolled, subject 02-001 will become 02-001-02 and so-on – the enrollment numbers are consecutive across both sites.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

4.5 Duration of Therapy

Study treatment with axitinib, avelumab, and bavituximab will continue until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

4.5 Treatment Beyond Progression

If a patient has evidence of progression per RECISTv1.1 while receiving axitinib, avelumab, and bavituximab, they will be permitted to continue the study treatment if they meet all the following criteria:

1) Evidence of clinical benefit or stability, as determined by the investigator following a review of all available data.
2) No significant, unacceptable, or irreversible toxicities related to the trial treatment.
3) No other treatment discontinuation criteria are met.
4) Absence of clinical disease progression including worsening symptoms or laboratory tests (such as new or worsening hypercalcemia) indicating unequivocal progression of disease.
5) Absence of decline in ECOG Performance Status that can be attributed to disease progression.
6) Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

Re-assessment of tumor burden must be no sooner than 4 weeks, but no longer than 9 weeks per iRECIST. Progressive disease is confirmed per iRECIST criteria and is evidenced by the appearance of more new lesions, increase size of prior new lesions (≥5 mm increase in sum of measures), or increase size of target and non-target lesions (≥5 mm increase in sum of measures). Patients with confirmed progressive disease per iRECIST will be permanently discontinued from the trial.

4.6 Duration of Follow Up

Ongoing adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event.

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months up to 2 years, until death, loss to follow-up, or until study termination by the Sponsor.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.4 apply. Notify the Principal Investigator and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 Informed Consent

Patients must provide a signed informed consent form prior to any study specific evaluations including screening.

5.1.2 Medical history

Complete medical and surgical history, and history of infections. Any ongoing sign/symptoms at registration should be assessed and graded per CTCAE, and followed as per Section 7.

5.1.3 Demographics

Documentation of demographic data will include age, sex, race, and self-reported race/ethnicity.

5.1.4 Review subject eligibility criteria

Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 3.

5.1.5 Review previous and concomitant medications

5.1.6 Physical exam including vital signs, height, and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, and weight.

5.1.7 Performance status

Performance status evaluated prior to study entry according to the ECOG Scale of Performance Status.

5.1.8 Hematology

Complete blood counts with differential.

5.1.9 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Other labs include TSH, free T3 and T4, AFP, and lipase

5.1.10 Coagulation tests

aPTT, PT/INR.

5.1.11 Hepatitis B and C testing

HBsAg, HBcAb, anti-HCV, HBV DNA, and HCV RNA

5.1.12 Urinalysis

5.1.13 Pregnancy test (for females of child-bearing potential)

Urine or serum pregnancy test.

5.1.14 Tumor assessment

Baseline tumor burden will be assessed by CT chest/abdomen/pelvis with contrast or MRI abdomen/pelvis with contrast and CT chest with or without contrast according to RECIST version 1.1.

5.1.15 Archival tumor tissue

Request archival tumor tissue (FFPE Block or 10-15 slides).

5.2 Procedures During Treatment

5.2.1 Day 1 of each cycle

- Physical exam, vital signs
- Weight
- Serum Pregnancy Test
- ECOG performance status
- CBC with differential
- CMP
- PT/INR
- aPTT
- TSH, free T3, free T4
- HBV DNA (every four cycles beginning cycle 5) if HBsAg, HBcAb, or HBV DNA are positive at time of screening.
- HCV RNA (every four cycles beginning with cycle 5) if anti-HCV and HCV RNA are positive at the time of screening.
- AFP
- Lipase
- Urinalysis
- Review AEs
- Medication Review
- Drug Accountability/ Pill Diary Review

5.2.2 Day 8, 15, 22 of each cycle

- Vital signs
- CMP (only on Day 15)
- Weight
- Medication Review
- Review AEs

5.2.3 End of treatment

- Physical exam, vital signs
- ECOG performance status
- Serum Pregnancy Test
- CBC with differential
- CMP
- PT/INR
- aPTT

- AFP
- Lipase
- Urinalysis
- Medication Review
- Review AEs
- Drug Accountability/Pill Diary Review
- Tumor Measurements

5.2.4 30 days after treatment termination

- Physical exam, vital signs
- CBC with differential
- CMP
- PT/INR
- aPTT
- TSH, free T3, free T4
- AFP
- Urinalysis
- Review AEs
- ECOG Performance Status
- Pregnancy Test

5.2.5 90 days after treatment termination

- Physical exam, vital signs
- CBC with differential
- CMP
- PT/INR
- aPTT
- TSH, free T3, free T4
- Urinalysis
- Review AEs
- ECOG Performance Status

5.2.6 Survival follow up

- Survival

5.3 Time and Events Table

Trial Period:	Screening	Treatment				End of treatment[a]	Follow-up		
		D1	D8	D15	D22		30-day post last dose	90-day post last dose	Survival follow up[j]
Scheduling window	-28 to -1	±3	±3	±3	±3	±7	±7	±7	±7
Administrative procedures									
Informed consent[b]	X								
Inclusion/exclusion criteria	X								
Medication review	X	X[c]	X	X	X	X			
Demographics	X								
Request archival tissue (FFPE block or 10-15 slides)	X								
Drug Accountability/Pill Diary		X				X			
Clinical Procedures									
Medical history including cancer, surgical and infections	X								
Vital signs	X	X	X	X	X	X	X	X	
Height	X								
Weight[d]	X	X	X	X	X				
Complete physical exam	X	X[c]				X	X	X	
Review AEs		X[c]	X	X	X	X	X	X	
ECOG performance Status	X	X[c]				X	X	X	
Tumor measurements[e]	X	Every 8 weeks				X			
CMP[f]	X	X[c]		X		X	X	X	
CBC with differential[f]	X	X[c]				X	X	X	
HBV and HCV serologies	X								
HBV DNA and/or HCV RNA[f]	X	Every four cycles beginning C5[g]							
Alpha-Fetoprotein (AFP)	X	X[c]				X			
Lipase	X	X[c]				X			
aPTT, PT/INR[f]	X	X[c]				X	X	X	
Urinalysis[f]	X	X[c,h]				X	X	X	
TSH, free T3, free T4	X	X[c]					X	X	
Pregnancy test[f,i]	X	X[c]				X	X		
Survival follow-up								X	X
Drugs									
Avelumab		X		X					
Axitinib		Taken continuously twice daily							
Bavituximab		X	X	X	X				

[a] Date of treatment discontinuation or withdrawal.

[b] Written informed consent can be obtained up to 30 days prior to study entry and is required before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests. Screening local

laboratory assessments obtained ≤96 hours prior to the initiation of study treatment do not have to be repeated for Cycle 1 day 1.
[c] Medication review, physical exam, review of AEs, ECOG performance status, and laboratories may be obtained ≤72 hours before Day 1 of each cycle.
[d] The dose of avelumab and bavituximab will be based on the patient's weight measured ≤14 days prior to baseline (the initiation of study treatment) and will remain the same throughout the study unless there is a weight change of >10% from baseline.
[e] Tumor assessments should be performed as close as possible to 8 weeks ± 1 week. Baseline tumor burden will be assessed by CT chest/abdomen/pelvis or MRI abdomen/pelvis and CT chest according to RECIST version 1.1. It is recommended that the same modality be used for all tumor assessments.
[f] Laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle. Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, total bilirubin, lipase, HBV DNA (if relevant), and HCV RNA (if relevant).
[g] HBV DNA (every four cycles beginning with cycle 5) is only tested if HBsAg, HBcAb, or HBV DNA are positive at time of screening. HCV RNA (every four cycles beginning with cycle 5) is only tested if anti-HCV and HCV RNA are positive at the time of screening.
[h] If urinalysis shows ≥2+ proteinuria, patient should undergo a 24-hour urine collection.
[i] Applicable to female of child-bearing potential as defined in Section 3.1. Serum pregnancy test must be performed on Day 1 of each cycle.
[j] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months up to 2 years until death, loss to follow-up, or until study termination by the Sponsor. Survival follow-up to start 3 months after 90-Day post last dose visit.

5.4 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

1) Subject voluntarily withdraws from treatment (follow-up permitted).
2) Subject withdraws consent (termination of treatment and follow-up).
3) Subject is unable to comply with protocol requirements.
4) Subject demonstrates clinical or radiographic evidence of disease progression based on Investigator assessment (note, continued treatment with study drug/treatment including treatment beyond RECIST 1.1 progression is deemed appropriate at the discretion of the investigator, but patients must discontinue trial treatment if progression is confirmed based on iRECIST).
5) Subject experiences toxicity that makes continuation in the protocol unsafe.
6) Treating physician judges that continuation on the study would not be in the subject's best interest.
7) Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event).
8) Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study.
9) Lost to follow-up. If a research subject cannot be located to document survival after a period of 6 months, the subject may be considered "lost to follow-up".

5.5 Reporting of Pregnancy and Lactation to Sponsor (UT Southwestern)

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

6.0 Measurement of Effect

6.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) Committee [Eur J Cancer. 2009;45(2):228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

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

6.1.2 Disease Parameters

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

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph

nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

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

Target lesions.
All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions.

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

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CT of the abdomen and pelvis or MRI of the abdomen and CT chest (if indicated as determined by the Investigator) should be done every 8 weeks ± 1 week.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

6.1.4.2 Evaluation of Non-Target Lesions

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.1.4.3 Evaluation of Best Objective Response

The best objective response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Objective response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Objective response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

6.1.5 Duration of Response

Duration of objective response: The duration of objective 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).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.2 Safety/Tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 5.0 for reporting of adverse events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

A safety lead-in phase composed of the first six patients evaluable for dose-limiting toxicities as defined in Section 4.2 will be performed to ensure the safety and tolerability of this triplet regimen.

7.0 ADVERSE EVENTS

7.1 Axitinib

For the most recent safety update, please refer to the current axitinib investigator's brochure.

7.1.1 Contraindications

None

7.1.2 Special Warnings and Precautions for Use

Aneurysms and artery dissections
VEGF pathway inhibitors may promote the formation of aneurysms and/or artery dissections. Before initiating axitinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Elevation of Hemoglobin or Hematocrit
Increases in hemoglobin or hematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib. An increase in red blood cell mass may increase the risk of thromboembolic events.

Hemoglobin or hematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If hemoglobin or hematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease hemoglobin or hematocrit to an acceptable level.

Gastrointestinal Perforation and Fistula Formation
In pooled clinical studies with axitinib for the treatment of patients with renal cell carcinoma, gastrointestinal perforation and fistula were reported in 13/672 patients (2%) receiving axitinib. Monitor for symptoms of gastrointestinal perforation periodically throughout treatment with axitinib.

Wound Healing Complications
In the Phase 3 study A4061032 with axitinib for the treatment of patients with renal cell carcinoma, all-causality adverse events suggestive of wound healing complications were reported in 4/359 patients (1%). Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible Posterior Leukoencephalopathy Syndrome
In pooled clinical studies with axitinib for the treatment of patients with renal cell carcinoma, reversible posterior leukoencephalopathy syndrome was reported in 2/672 patients (<1%) receiving axitinib. In patients with signs/symptoms of reversible posterior leukoencephalopathy syndrome, axitinib should be permanently discontinued.

Heart failure events
In a controlled clinical study with axitinib for the treatment of patients with Renal Cell Carcinoma (RCC), heart failure events were reported in 1.7% of patients receiving axitinib. Grade 3/4 and 5 cardiac failure events were observed in 0.6% and 0.6% of patients receiving axitinib, respectively. Monitor for signs or symptoms of cardiac failure periodically throughout treatment with axitinib.

Hypertension
In pooled clinical studies with axitinib for the treatment of patients with renal cell carcinoma , hypertension was reported in 51% of patients receiving axitinib. Grade 3 and 4 hypertension was reported in 22% and 1% of patients receiving axitinib, respectively.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. For persistent hypertension despite use of anti-hypertensive medications, axitinib dose should be reduced. For severe hypertension, axitinib should be held and resumed at a lower dose level once

hypertension is improved. If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Thyroid dysfunction
In clinical studies with axitinib for the treatment of patients with Renal Cell Carcinoma (RCC), hypothyroidism was reported in 25% of patients receiving axitinib. Hyperthyroidism was reported in 2% of patients receiving axitinib. Monitor thyroid function before initiation of, and periodically throughout treatment with axitinib. Hypothyroidism and hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial thromboembolic events
In clinical studies with axitinib for the treatment of patients with Renal Cell Carcinoma (RCC), arterial thromboembolic events were reported in 3% of patients receiving axitinib. Grade 3 events were reported in 1% and Grade 4 events were reported in 1% of patients.

Axitinib should be used with caution in patients who are at risk for, or who have a history of these events.

Venous thromboembolic events
In clinical studies with axitinib for the treatment of patients with Renal Cell Carcionma (RCC), venous thromboembolic events were reported in 3% of patients receiving axitinib. Grade 3 and 4 venous thromboembolic events were reported in 2% of patients.

Axitinib should be used with caution in patients who are at risk for, or who have a history of these events.

Hemorrhage
In clinical studies with axitinib for the treatment of patients with Renal Cell Carcinoma (RCC), hemorrhagic events were reported in 26% of patients receiving axitinib. Grade 3 and 4 hemorrhagic events were reported in 3% and 1% of patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Proteinuria
In clinical studies with axitinib for the treatment of patients with Renal Cell Carcinoma (RCC), proteinuria was reported in 21% of patients receiving axitinib. Grade 3 and 4 proteinuria were reported in 5% and <1% of patients receiving axitinib, respectively. Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment.

Hepatic impairment
A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Monitor ALT, AST and bilirubin before initiation of and periodically throughout treatment with axitinib.

7.1.3 Interaction with other medications

Axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1. Inhibitors of CYP3A4/5 such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin may

increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib by approximately half is recommended.

Strong inducers of CYP3A4/5 including rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, and Hypericum perforatum (St. John's wort) may decrease axitinib plasma concentrations. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended.

7.1.4 Adverse Reactions

The following side effects are suspected to be related to axitinib treatment for reporting purposes:

- Cardiac failure events (cardiac failure, cardiopulmonary failure, left ventricular dysfunction, and right ventricular failure)
- Palmar-plantar erythrodysesthesia
- Hypertension
- Aneurysms and artery dissections
- Thyroid dysfunction
- Arterial thromboembolic events
- Venous thromboembolic events
- Increased Hemoglobin/hematocrit
- Hemorrhage
- Gastrointestinal perforation
- Wound healing complications
- Posterior reversible encephalopathy syndrome
- Proteinuria
- Diarrhea
- Increased serum creatinine

7.2 Avelumab

7.2.1 Contraindications

None

7.2.2 Special Warnings and Precautions for Use

<u>Infusion related reactions</u>
Avelumab can cause severe or life-threatening infusion reactions. Patients should be premedicated with antihistamine and acetaminophen prior to infusions. Monitor patients for signs and symptoms including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate Infusion-Related Reactions (IRRs). Stop the infusion and permanently discontinue avelumab for severe (Grade 3) or life-threatening (Grade 4) infusion reactions.

<u>Immune related AEs (irAEs)</u>
Avelumab treatment may result in severe and rarely fatal immune-related toxicities. irAEs may affect any organ causing pneumonitis, hepatitis, colitis, dermatitis/rash, endocrinopathies, myalgias/arthralgias, or nephritis. Less

frequent irAEs include myositis, myocarditis, hypophysitis, uveitis, myasthenia gravis, and Guillan-Barre syndrome. For suspected immune-related adverse reactions, evaluation should include investigations to rule out non-immune causes of symptoms. Depending upon the severity of the adverse reaction, Avelumab may be delayed or permanently discontinued. Depending on the type of irAE, management may include hormone supplementation, corticosteroids, non-steroid immunosuppressants, or biologic agents.

7.2.3 Interaction with other medications

No interaction studies have been conducted with avelumab in humans.

7.2.4 Adverse Reactions

The following side effects are suspected to be related to avelumab treatment for reporting purposes:

- Infusion reaction
- Hypothyroidism
- Adrenal insufficiency
- Hyperthyroidism
- Hypothyroidism
- Hypopituitarism
- Uveitis
- Colitis
- Autoimmune hepatitis
- Pancreatitis
- Type 1 diabetes mellitus
- Myositis
- Guillan-Barre syndrome
- Nephritis
- Pneumonitis
- Rash/dermatitis

7.3 Bavituximab

7.3.1 Contraindications

Known allergy or hypersensitivity to any component of the drug product or prior Grade ≥3 infusion reaction, hypersensitivity, or anaphylaxis after receiving any other monoclonal antibody therapy.

7.3.2 Special Warnings and Precautions for Use

Infusion related reactions

Bavituximab can cause infusion reactions. Monitor patients for signs and symptoms including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate IRRs. Stop the infusion and permanently discontinue bavituximab for severe (Grade 3) or life-threatening (Grade 4) infusion reactions.

7.3.3 Interaction with other medications

Potential drug-drug interactions between bavituximab and docetaxel were investigated in 17 patients, which showed no significant differences in PK parameters when bavituximab was administered with or without docetaxel.[42]

7.3.4 Adverse Reactions

No adverse reactions are known to be specifically attributable to bavituximab. All serious adverse events will be reported to the Sponsor.

7.4 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are assessed in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.4.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical, and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;

- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is, by definition, an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24-hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.4.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.5 Expedited Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

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

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.5.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information to the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if

further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Investigator: David Hsieh Phone: 214-648-4180 Research Manager: Ellen Siglinsky Phone: 214-648-7031
Written reports to: Investigator: David Hsieh Email: david.hsieh@UTSouthwestern.edu Fax: 214-648-8146 Research Manager: Ellen Siglinsky Email: ellen.siglinsky@UTSouthwestern.edu Fax: 214-648-1906 UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of study team awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance/

7.6 Stopping Rules

This study utilizes a two-stage design which allows stopping for futility which minimizes the expected sample size when the true response is low. In the first stage, 14 evaluable patients will be accrued. The study will procced to the second stage only if 2 or greater responses are observed. If less than 2 responses are observed among the first 14 evaluable patients, the study will be terminated.

8.0 DRUG/TREATMENT INFORMATION

8.1 Axitinib

- Other names for the drug(s): Inlyta
- Classification - type of agent: Targeted therapy
- Mode of action: Selective inhibitor of VEGFR-1, 2, and 3
- Storage and stability: Axitinib must be stored at controlled room temperature (between 15-30 C) or as specified in the product label.
- Protocol dose: 5 mg BID at approximately the same time in the morning and evening on a continuous dosing schedule. Axitinib tablets are to be taken approximately 12 hours apart and may be administered without regard to meals. Tablets must not be crushed, split, or dissolved, and patients should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing. A dosing card will be provided to the patients to provide guidance for the correct use of axitinib.
- Route of administration for this study: oral
- Availability: provided by Pfizer

- Side effects: The most common (≥20%) adverse reactions observed following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysesthsia, hemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation. See Section 7.1.4 and the axitinib Investigator's Brochure for additional information on expected treatment related AEs.

8.1.1 Return and Retention of Study Drug

Patients will be required to return to the investigational site all bottles of axitinib every 4 weeks (at the end of each cycle) during the planned visit at the site. The number of remaining axitinib tablets will be documented and recorded at each clinic visit. The patient diary may also be used to support this part of the axitinib accountability process.

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

8.1.2 A dosing card will be provided to the patients to provide guidance for the correct use of axitinib. Patients must be instructed that if they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken late, up to 3 hours before the next scheduled dose of that day, otherwise, it should be skipped and dosing resumed with subsequent doses as prescribed. Patient must be instructed to record all doses (missed or vomited doses or extra doses) in a dosing diary supplied by the site.

8.2 Avelumab

- Other names for the drug(s): Bavencio
- Classification - type of agent: Immunotherapy
- Mode of action: anti-PD-L1 antibody
- Storage and stability: Store at 2°C to 8°C and protected from light until use. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.
- Protocol dose: 10 mg/kg every 2 weeks (maximum dose of 2000)
- Route of administration for this study: intravenous
- Avelumab will be dosed at the investigational site. Avelumab will be administered as a 1-hour (no longer than 2 hours) IV infusion on Day 1 and Day 15 of each 28-day cycle. Avelumab may be administered up to 3 days before or after the scheduled Day 1 of each dose due to administrative reasons. Avelumab should be administered at least 30 minutes after the bavituximab infusion (on days when both are administered). In order to mitigate infusion-related reactions, a required premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen will be administered immediately prior to administration of avelumab.

- The contents of the avelumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products. Avelumab drug product must be diluted with preferably 250 mL 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively, a 0.45% saline solution can be used if needed. If not used immediately, the diluted drug product can be stored up to 8 hours at room temperature or up to 24 hours at 2°C to 8°C. The storage conditions may be limited to up to 4 hours at room temperature depending on the approved avelumab label in the country. No other drugs should be added to the solution for infusion containing avelumab.

  Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Dosage and Administration Instruction contained in the Investigational Product Manual (IP Manual).

- Availability: provided by Pfizer

- Side effects: The most frequent AEs attributable to avelumab include infusion reactions and irAEs. See Section 7.2.4 and the avelumab Investigator's Brochure for additional information on expected treatment related AEs.

8.2.1 Return and Retention of Study Drug

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

8.3 Bavituximab

- Other names for the drug(s): none

- Classification - type of agent: Immunotherapy

- Mode of action: anti-phosphatidylserine antibody

- Storage and stability: Store at 2°C to 8°C. Once diluted, it should be stored at room temperature and used within 8 hours.

- Protocol dose: 3 mg/kg every week

- Route of administration for this study: intravenous

- Bavituximab will be dosed at the investigational site. Infusion preparation and administration are to be performed as follows:

  1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used). Fill treatment into a sterile glass bottle or plastic IV bag.
  2. Using aseptic techniques, repeat procedure until the calculated volume has been put into the container. Bring the final volume to 100 mL using 0.9% Sodium Chloride Injection, USP.

3. Administer through a low protein binding 0.2-micrometer in-line filter (placed as proximal to the patient as practical).
4. Affix the infusion line and prime it with infusate before starting the infusion. Infuse the solution intravenously over 90 (± 10) minutes. No reduction in infusion time will be permitted. Flush the line with normal saline after infusion.

- Availability: provided by OncXerna

- Side effects: The most frequent AEs attributable to bavituximab include decreased appetite, fatigue, constipation, nausea, and diarrhea. See Section 7.3.4 for additional information on expected treatment related AEs.

8.3.1 Return and Retention of Study Drug

The sponsor or designee will provide guidance on the destruction of unused investigational product. 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 OncXerna, and all destruction must be adequately documented.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to assess genetic mechanisms of immunotherapy resistance. Analyses will be performed on tissue specimens collected as a component of routine clinical practice, and thus no additional specimen collection solely for research purposes is required.

Archival or baseline tumor tissue will be genomically characterized by MI Profile (Caris Life Sciences). This will allow us to assess whether mutations, copy number alterations, and RNA signatures may be associated with different clinical outcomes.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

The study is an open-label, non-randomized single-arm, multi-center phase II therapeutic clinical trial with a safety lead-in. The study population will be patients with advanced HCC.

Combination treatment with axitinib, avelumab, and bavituximab will be tested in a safety lead-in of the first 6 patients evaluable for dose-limiting toxicities in this study (see definitions for evaluable patients and dose-limiting toxicities in Section 4.2) to ensure the safety and tolerability of this triplet regimen.

A two-stage design is used to limit the maximum sample size required to determine efficacy. Objective response requires confirmation imaging greater than or equal to 4 weeks after initial best response. Patients who attain a complete response, partial response, or stable disease but do not have two imaging assessments to confirm response will be replaced. Patients who have progressive disease at any imaging assessment do not require subsequent confirmation.

10.2 Sample Size and Accrual

We will use a minimax two-stage design method to compare the objective response rate of 34% (alternative hypothesis) for the treatment cohort versus 14% (null hypothesis) for the historical control. The basis of the null response rate is based on the previously reported objective response rate of 14% for axitinib plus avelumab in advanced HCC. This design

requires a sample size of 29 evaluable patients to yield a type I error rate of 0.10 and power of 0.9 when the true response rate is 34%. In the first stage 14 evaluable patients will be accrued. If there are 2 or more responses, then 15 additional evaluable patients will be accrued. Thus, the total enrollment for this study will be up to 29 evaluable patients. The null hypothesis will be rejected if 7 or more responses are observed in 29 patients. Objective response rate is defined as number of responders (either complete or partial response as the best objective response) of eligible patients. Patients who attain a complete response, partial response, or stable disease but do not have two imaging assessments to confirm response will be replaced.

10.3 Data Analyses

Objective response rate, and disease control rate with corresponding 2-sided 95% CIs will be estimated using the Clopper-Pearson method. Kaplan-Meier methods will be used to estimate medians and 95% CIs for duration of response, overall survival, and progression-free survival. Survival outcomes will be calculated from Day 1 of Cycle 1. Descriptive statistics will be used to analyze AEs described according to the NCI CTCAE v5.0. Clinically significant laboratory abnormalities will be described as well. Serious adverse events will be summarized, including a causality assessment. The number of treatment cycles and doses administered will be summarized using descriptive statistics.

Associations between molecular features and tumor response will be analyzed using the Fisher-exact test with Benjamini-Hochberg multiple-testing correction. Cox regression models will be used to assess for associations between overall survival or progression-free survival and exploratory and correlative measures.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any sub-site, the following documentation must be provided to the UTSW Clinical Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal-wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UTSW holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract
- Signed Monitoring Plan

11.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed.

Trial monitoring will be conducted according to the study specific monitoring plan. This will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the UTSW Simmons Cancer Center Gastrointestinal Disease-Oriented Teams (GI DOT), which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity and dose escalation reviews will be performed in real-time by the GI DOT and DSMC. These reviews will be documented by distributing reports of the findings to the members of the GI DOT and investigators.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level

of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

 Reporting requirement*: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

11.5.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

 Reporting requirement*: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

11.5.3 Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)

 Reporting requirement*: Serious Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.5.4 Continuing Noncompliance: includes a pattern of repeated noncompliance which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

 Reporting requirement*: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.5.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance
  Reporting requirement*: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first.

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

Appendix A: Drug diary

SUBJECT DOSING DIARY

SITE STAFF INSTRUCTIONS (**prior to** providing to subject):

- Complete the header and footer of each page (one page per week) of the diary. The subject should be instructed to complete the dosing diary table(s).
- Complete the contact details at the bottom of this cover page with the name and phone number for the best contact person for subject inquires.
- It is important to train the subject on correct completion of this diary. For the first dose on Cycle 1 Day 1 training must be completed.
- Ensure the subject understands this diary should be completed daily and brought to the clinic at each visit along with all used bottles of Axitinib.

SUBJECT INSTRUCTIONS

Diary Instructions:

- This is a "diary" that you will use to keep track of daily dose amounts, when you take your doses. Each page represents 1 week of dosing, so you should complete 4 pages for each 28-day cycle.
- It is important that you fill out this diary (using pen) every time you take a dose. Record the day of the week, date, time, and number of tablets taken for each dosing.
- **You must bring this diary and all used bottles to the clinic at each visit**. It is important that you keep the diary and bottles in a safe place where they will not be lost.

Dosing Instructions:

- Axitinib should be taken at approximately the same time(s) each day and may be administered without regard to meals or other medications.
- Tablets should not be crushed, split, or dissolved – swallow whole.
- If you miss a dose of Axitinib you must follow these guidelines:
  - A missed dose may be taken late, up to 3 hours before the next scheduled dose that day. Otherwise, skip and resume dosing with next scheduled dose.
  - If you vomit at any time after taking a dose, do not "make it up". Continue taking Axitinib as scheduled.
  - Record all doses – including missed or vomited – on the dosing diary.
- **If a surgery or an interventional procedure is planned, you will need to discuss this with your doctor because Axitinib may need to be temporarily held for safety reasons.**
- If you have any questions, please contact the clinic staff at:

_____ _____

Name / Study Coordinator *Telephone*

For Clinical Trial Use Only. Keep out of reach of children. Maintain tablets in original bottles.

Confidential

Dosing Diary Version 2 - 20Apr2022

IRB # 2022-0116

Year ___ ___ ___ ___

Cycle ____ Week ____

Subject ID:	
Dose Assigned:	_____ mg BID (Twice Daily)
# of Tablets per Dose	

Instructions: Take the specified number of tablets (upper right) and record each day in the dosing diary/table below.

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Day of Week							
	Date							
First Dose	Were Prescribed # of Tablets Taken?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
	# of Tablets Taken	_____	_____	_____	_____	_____	_____	_____
	Time of Dose	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM
Second Dose	Were Prescribed # of Tablets Taken?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
	# of Tablets Taken	_____	_____	_____	_____	_____	_____	_____
	Time of Dose	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM	__ __ : __ __ ☐ AM ☐ PM

Comments (Any missed doses/additional details for any doses above):

Confidential

Dosing Diary Version 2 - 20Apr2022
IRB # 2022-0116

Year ___ ___ ___ ___
Cycle ____ Week ____