MSK PROTOCOL COVER SHEET

TALAZOPARIB AND AVELUMAB IN GENOMICALLY DEFINED METASTATIC RENAL CELL CARCINOMA

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase II, open-label, single-institution trial to study the combination of talazoparib and avelumab in patients with advanced or metastatic renal cell carcinoma (RCC). This protocol leverages underlying genomic instability in three genomically defined RCC variants and pairs targeted immunotherapy with PARP inhibition.

RCC represents a heterogenous set of tumors distinguished by histology, molecular and genomic features. A hallmark of clear cell RCC, the most common histologic RCC subtype, is von Hippel Lindau *(VHL)* inactivation occurring in >90% of tumors. *VHL* acts as a hypoxic sense regulator and, amongst other functions, supports DNA repair and genomic integrity; consequently, *VHL* loss promotes genomic instability. Similar in effect, in two rare RCC subtypes characterized by loss-of-function mutations in fumarate hydratase (*FH*) and succinate dehydrogenase (*SDH*), downstream oncometabolite accumulation leads to DNA repair inhibition, resulting in genomic instability. Further, renal medullary carcinoma (RMC) also has been associated with high DNA replication stress. All of these settings (*VHL*, *FH/SDH* loss, and RMC) have been shown to render cancer cells vulnerable to PARP inhibitors. As DNA damage is thought to increase neo-antigen repertoires and innate immune effectors, paired PARP inhibition with immune checkpoint blockade may achieve additive and/or synergistic effects in both clear and non-clear cell cohorts with separate rationales.

This protocol investigates the use of talazoparib, a potent selective PARP inhibitor, and avelumab, an anti-PD-L1 monoclonal antibody blocker, in patients with advanced RCC. The protocol will enroll patients in two independent, non-randomized cohorts in parallel (Table 1). Cohort 1 will enroll patients with previously treated *VHL*-deficient RCC in a Simon two-stage design: if ≥1/10 patients achieve an objective response in Stage I, the trial will then continue to accrue a total of 29 patients for efficacy analysis. Cohort 2 will enroll 15 patients with advanced RCC and *FH*- or *SDH*- loss or medullary RCC, and analysis will be descriptive given disease rarity.

Cohort	Population	Target Enrollment	Talazoparib	Avelumab
1	*VHL*-deficient RCC	Stage I: 10 patients Stage II: 19 patients	1 mg daily PO	800 mg IV
2	*FH*-, *SDH*- deficient RCC, RMC	Total = 15 patients	1 mg daily PO	800 mg IV

Table 1. **Cohort Design**. VHL: von Hippel Lindau; FH: fumarate hydratase, SDH: succinate dehydrogenase, PO: oral, IV: intravenous

All patients will receive combination treatment at the previously established recommended phase II dose, 800 mg avelumab every 2 weeks with 1 mg talazoparib daily, in 28-day cycles. The primary endpoint will be objective response rate (ORR) measured by iRECIST. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and safety and tolerability of combination therapy. Exploratory endpoints for both

cohorts include analysis of expression-based biomarkers for tissue response, characterization of inflammatory recruitment responses, and oncometabolite analysis in cohort 2 patients.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Aim: To determine the objective response rate (ORR) of combination talazoparib and avelumab in all treatment cohorts by iRECIST.

Secondary aims will include:

1. To determine the progression-free survival (PFS) in all treatment cohorts by RECIST v1.1.
2. To determine the overall survival (OS) in all treatment cohorts by RECIST v1.1.
3. To evaluate the safety and tolerability, and compliance of combination talazoparib and avelumab in all treatment cohorts.

Exploratory aims will include:

1. **Cohorts 1 & 2:**
    a. To characterize DNA damage response pathways including homolgous recombination deficiency (HRD), large scale transition (LST) scores, inflammatory and microenvironment changes.
2. **Cohort 2:**
    a. To assess metabolomic changes and oncometabolite generation for Cohort 2.

3.0 BACKGROUND AND RATIONALE

3.1 Renal Cell Carcinoma Epidemiology

Renal cell carcinoma (RCC) is the most common and lethal form of kidney cancer, affecting over 65,000 each year in the United States with a rising incidence (*1*). The growing incidence of RCCs stems from modifiable risk factors including tobacco use, hypertension, and obesity, as well as a shift in incidental radiographic diagnoses in asymptomatic patients (*2*). As one-third of patients with RCC present with metastatic disease at diagnosis, and one-fourth of patients experience disease relapse following nephrectomy, there continues to remain a high unmet need for systemic therapy options for patients with advanced disease.

3.2 Renal Cell Carcinoma Subtypes

The World Health Organization (WHO) classifies sixteen distinct kidney cancer subtypes based on genomic, molecular, histologic and syndromic features (*3*). The most common RCC variant in the metastatic setting is clear cell RCC, accounting for ~75% of diagnoses, followed by other non-clear cell histologies like papillary, chromophobe, and unclassified tumors. Although these subtypes occur most commonly as sporadic cancers, many also occur in the syndromic setting with several familial syndromes characterized in terms of

germline alterations and ensuing pathobiology. Von Hippel Lindau (VHL) syndrome is characterized by bi-allelic *VHL* loss and the development of bilateral and multifocal clear cell RCCs with additional tumor developments including hemangioblastomas, pheochromocytomas, and neuroendocrine tumors. Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome usually manifests with papillary RCC tumors developing in the context of germline loss of fumarate hydratase (*FH*), and is characterized by the development of cutaneous leiomyomas, leiomyosarcomas and paragangliomas . Hereditary paragangliomas and paragangliomas (HPGL/PCC), characterized by germline loss of succinate dehydrogenase (*SDH*) is characterized by RCC as well as pheochromocytomas, paragangliomas, and gastrointestinal stromal tumor development. Renal medullary carcinoma (RMC) is a rare, lethal form of kidney cancer most notably associated with hemoglobinopathies and occurs mainly in young individuals and is highly refractory to systemic therapies that are successfully applied in other RCC variants .

3.3 Renal Cell Carcinoma Genomics

The genomic landscape for clear and non-clear RCC variants have been outlined through large-scale efforts with The Cancer Genome Atlas (TCGA) and the TRACERx study, helping uncover patterns within the context of clinical and tumor evolution (*4-6*). A hallmark event that characterizes >90% of clear cell RCCs is chromotripsis of chromosome 3p, with then subsequent gains in chromosome 5q and loss of 15q (*4*). Haploinsufficiency of *VHL* is insufficient for tumor growth and may precede RCC development by even decades (*7*), and secondary genomic or epigenetic events affecting *VHL* and other chromosome 3p genes are central to disease pathogenesis. Complete loss of pVHL, the encoded protein, leads to downstream accumulation of hypoxia inducible factor (HIF) proteins and transcriptional upregulation of HIF-dependent pathways that affect cell proliferation, cell migration, cell metabolism, and angiogenesis. Functional loss of *VHL* may be due to acquired point or frame mutations, as well as mutations in partnering proteins (i.e. TCEB1) and promotor methylation silencing (*8-10*).

While chromosome 3p loss remains the linchpin in characterizing clear cell RCC biology, other RCC variants (non-clear cell) harbor distinct genomic alterations that contribute to disease pathogenesis. This includes loss-of-function (LOF) mutations in *FH,* a gene that encodes for a Krebs cycle enzyme catalyzing the hydration of fumarate to malate, which can be lost in sporadic and syndromic papillary variants of RCC (*11*). *FH*- loss radically shifts metabolism to aerobic glycolysis obliging cells to become dependent on glycolysis for subsequent ATP production (*12*). Similarly, LOF mutations in *SDH,* a mitochondrial enzyme responsible for the oxidation of succinate to fumarate, also leads to metabolic dysregulation in other non-clear cell RCC entities. In addition, RMC tumors are almost uniformly characterized by SMARCB1 (INI1) (*13*), which functions as a subunit of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex and has been characterized with increased DNA replication stress (*14*).

Beyond these well understood mechanisms for clear cell (*VHL*-deficient) and other tumor subtypes (*FH / SDH*-deficient or *SMARCB1-loss* medullary), several recent reports have

highlighted each of these genes are integral to genomic maintenance described below, providing molecular rationale for the present study.

3.4 DNA-damage Response (DDR) Pathways

DNA repair is an essential mechanism for genomic integrity maintenance as unrepaired DNA damage ultimately leads to cell death or senescence. Minor alterations in DNA are corrected using base or nucleotide excision repair mechanisms, and more lethal DNA damage events like strand breaks (single or double) or complex events like interstrand cross-linking are usually repaired using two complex pathways: homologous recombination (HR) and non-homologous end joining (NHEJ) (*15*). HR retains the highest fidelity, as this process requires a template DNA strand for repair and ligation, whereas NHEJ relies on processing terminal end strands only for subsequent DNA ligation. Because of the template requirement, HR can only occur in certain cell cycle phases compared to NHEJ. DNA double strand breaks (DSBs) are particularly challenging as repair relies on the coordination of multiple pathways as detailed below.

Consequences of ineffective DNA repair have been highlighted through analysis of specific DNA damage response (DDR) pathway alterations found in several malignancies as well effects from cytotoxic DNA damaging chemotherapies. Multiple DDR pathways have been characterized with specific components (*16*) including:

1. Nucleotide Excision Repair (NER): *ERCC1/2/34/5/6/8, DDB1/2, RPA1/2/3, XPC, RAD23B, CETN2, GTF*
2. Mismatch Repair (MMR): *MLH1, MSH2, MSH6, PMS1/PMS2*
3. HR: *BRCA1/2, PARP1, ATM, ATR, RAD51C, BAP1, PALB2, MRE11A/NBN, BARD1/BRIP1, RAD50/51/51B/51D*
4. NHEJ: *PRKDC, XRCC5/6, LIG4, XRCC4, NHEJ1*
5. Others: *FANCC, FANCA, BLM, CHEK1/2, POLE, ATRX, ATR, RAD1, HUS1, TP53, RIF1, CLK2, TOPB1, PER1*

Loss of one or more DDR pathways may lead to increased cancer predisposition (i.e. *BRCA* or *ATM* mutant malignancies), as well as enhanced susceptibility to DNA damage therapies through “synthetic lethality” (*17*). This has been exploited recently through PARP inhibition in patients with underlying *BRCA* germline mutations in multiple tissue models (*18-22*). Additionally, other DDR losses like MMR deficiency have been shown to have higher mutational load correlating with improved response to immune checkpoint blockade therapy (*23*).

3.5 *VHL*-deficiency and Genomic Maintenance

Besides promotion of the adaptive pseudohypoxia response through HIF-dependent pathways, *VHL* plays an integral role in other cellular processes including extracellular matrix regulation, microtubule stabilization, and cell cycle regulation through DNA repair and regulation of apoptosis and senescence (*24, 25*). Interestingly, pre-clinical work highlights that *VHL* loss increases DNA damage and replication stress, with increases in

ATR (*ATM* and *RAD-3* related), *CHK1*, and replication fork stalling, all of which contribute to increased genomic instability, replication mechanism collapse, and cell cycle arrest (*26*). In addition, *VHL*-deficient RCC cells also show impaired NER capacities as well (*27*).

BRCAness, the notion that DDR associated genes other than *BRCA1* and *BRCA2* confer similar defects in DNA repair, has increasingly been applied in many tumor models and genes (*28*). Interestingly, an analysis of RCC tumors with associated tumor thrombus, a common and poor prognostic feature, has also highlighted that many RCC tumors have conferred BRCAness. Based upon identification of BRCAness mutational signatures in this select population with associated tumor thrombus, investigators re-analyzed 400 patients in the TCGA clear cell RCC cohort irrespective of tumor thrombus and identified high predominance of a BRCAness mutational signature, accounting for 74.25% of patients (297/400 samples) (*29*).

VHL-deficient clear cell RCCs have shown to have lower expression of HR and MMR genes, with 30-60% reductions of mRNA levels of *BRCA1, RAD51, MLH1,* and *FANCD2* compared with VHL-wildtype tumor cells (*30*). Expression changes were confirmed upon TCGA interrogation, and *VHL*-loss specifically was associated with impaired DNA DS break repair, conferring a BRCAness phenotype (*31*). Based on the above studies, this BRCAness phenotype is associated with a majority of clear cell RCCs.

3.6 PARPi and RCC

Poly(ADP-ribose) polymerase (PARP) are enzymes that activate upon damaged DNA binding, with further functions including: detection of single-stranded and DS breaks, recruitment of DNA repair machinery and replication formation at the injured site. PARP is usually upregulated during replication stress, with DDR pathway signal transduction and protein complex modification through PARylation (*32*).

The concept of exploiting synthetic lethal interactions between inherently impaired DNA repair and PARP inhibitors (PARPi) has proven successful in human malignancies. For instance, as functional BRCA1/2 proteins are integral for DSB repair, *BRCA1/2* mutants are increasingly vulnerable to PARPi with significant clinical responses in this genomically defined population. Interestingly, treatment with niraparib has shown clinical benefit in patients irrespective of *BRCA* status (*BRCA* wild-type or mutant), and significant clinical effects were seen in patients with HR deficient tumors also irrespective of BRCA status (*21*). In total, the FDA has approved multiple agents across tumors in mostly BRCA mutant populations (Table 2), and further exploration of other DDR pathway mutants including those tumors with BRCAness remains underway.

PARPi	FDA Approved Indications
Rucaparib	1. Treatment of advanced stage, BRCA1/2 mutant ovarian cancer refractory to ≥2 prior lines of therapy 2. Maintenance for advanced stage, recurrent ovarian cancer in CR or PR after platinum-based chemotherapy
Niraparib	1. Maintenance for patients with advanced stage ovarian cancer who are in CR or PR after platinum-based chemotherapy

Olaparib	1. Maintenance therapy for advanced stage, recurrent ovarian cancer in CR or PR after platinum-based chemotherapy 2. Treatment of advanced stage, BRCA1/2 mutant ovarian cancers refractory to ≥3 prior lines of therapy. 3. Treatment for metastatic HER2 negative, BRCA1/2 mutant breast cancer refractory to chemotherapy
Talazoparib	1. Treatment of BRCA mutated, HER2 negative locally advanced or metastatic breast cancer

Table 2: FDA Approved PARPi in 2018: PARPi=PARP inhibitor; CR=complete response; PR=partial response

Interestingly, tumor hypoxia leads to repression of DNA repair through both HIF-dependent and independent mechanisms with suppression of multiple repair mechanisms including *BRCA1/2* (*33*), and cells without intrinsic DNA repair defects are increasingly sensitive to PARPi in hypoxic microenvironments (*34*). In RCC, where tumors have hypoxic pathway upregulation through HIF dependent pathways, pre-clinical evidence has also shown that clear cell RCCs are sensitive to the PARP inhibitor olaparib, with evidence of subsequent increase in replication stress, suppression of DNA synthesis, and eventual cell cycle arrest. RCC cells that also harbor *BAP1* mutations, a known secondary chromatin modifying gene mutation with aggressive clinical courses, have also shown increased sensitivity to the PARP inhibitor olaparib (*35*). In line with supportive evidence of PARPi in BRCAness tumors, *VHL*-deficient cells were sensitive to PARPi olaparib and talazoparib when compared with *VHL*-wild type cells (*30*).

Interestingly, germline and somatic loss of *FH* and *SDH* also contribute to genomic instability through accumulation of oncometabolites and HR suppression. Recently, these specific mutations have been shown to lead to accumulation of fumarate and succinate respectively, resulting in inhibition of α-ketoglutarate (αKG)-dependent dioxygenases and eventual accumulation of DNA DSBs through HR impairment and activation of DDR pathways (*36*). Taken a step further, *FH*- and *SDH*- deficient tumors were also found to be sensitive to the PARP inhibitors olaparib and talazoparib *in vitro* and *in vivo*. Selected results regarding tumor xenograft models of *FH*- and *SDH*- knockdown in nude mice are displayed below (*36*).

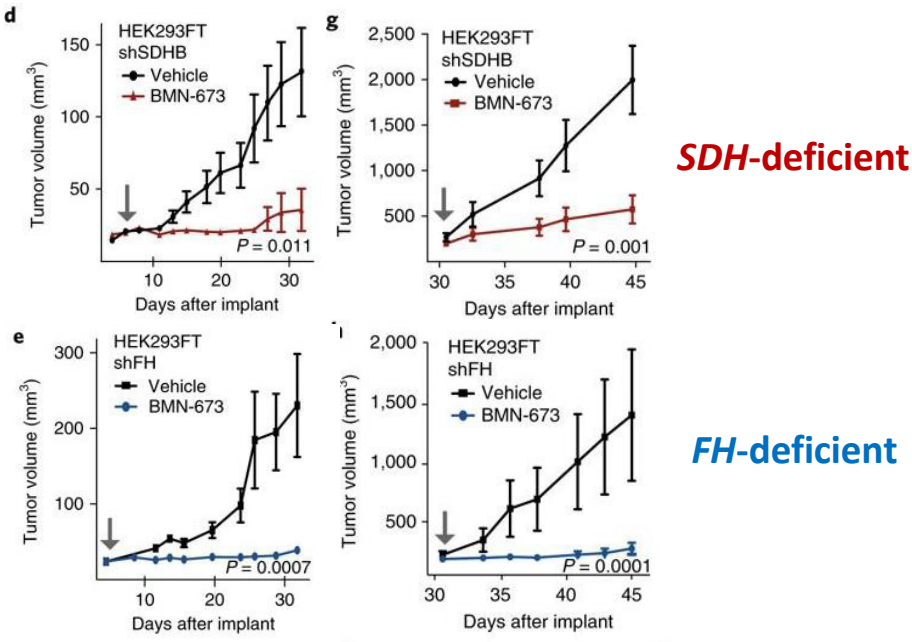

Figure 1: FH- and SDH- Sensitivity to Talazoparib: Nude mice tumor xenografts were implanted with *FH*- and *SDH*-deficient cell lines by shRNA knockdown versus vehicle control. Treatment with talazoparib (BMN - 673) resulted in significantly delays in growth after tumor implantation. Adapted from (*36*).

RMC tumors which are characterized for SMARCB1-loss have also been proposed to be sensitive to PARPi therapeutic strategy. Firstly, *in vitro* growth of SMARCB1-loss cell lines have been shown to be inhibited to olaparib and this drug sensitivity appeared more profound when compared to *BRCA1*-mutant cell lines (HCC1395 and HCC1937) (*14*). Moreover, RMC cell lines shown sensitivity to both olaparib and niraparib, and a patient derived xenograft (PDX) RMC model demonstrated that niraparib treatment led to a significant reduction in tumor volume *in vivo* (Figure 2). (*14*)

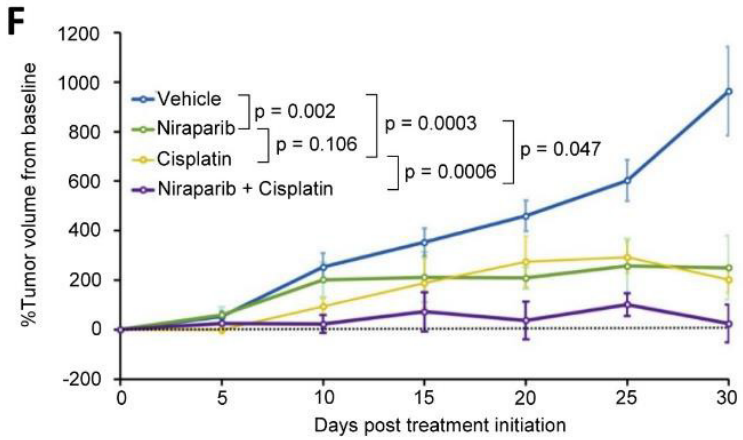

Figure 2: RMC Sensitivity to PARPi. A RMC PDX model was generated using banked implanted tumor tissue implanted into subcutaneous tissue of immunodeficient mouse. Treatment with niraparib (PARPi) led to regression in tumor volume compared to vehicle control. Adapted from (*14*).

3.7 Treatment Paradigms for Metastatic RCC

Current systemic therapies used for patients with metastatic RCC include vascular endothelial growth factor (VEGF) targeted agents, immune checkpoint blockade (ICB), and targeted agents against the mTOR pathway. Currently, no predictive biomarker has been identified to aid in therapy selection, and treatment is clinically determined based upon disease risk assessed by nomograms like the MSKCC and International Database of Metastatic RCC (IMDC) (*37, 38*). Both risk models include clinical and laboratory markers which correlate with disease prognosis and ultimately stratify patients into favorable, intermediate or poor-risk disease.

Based on results from CheckMate-214, a randomized phase III study of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) versus sunitinib in patients with metastatic clear cell RCC, combination ICB is superior in patients with intermediate and poor-risk disease with improved overall survival (HR=0.53) and objective response rates (42% ICB versus 27% sunitinib) (*39*). In the second-line setting, nivolumab monotherapy is also superior to everolimus (*40*), and subsequent lines of therapy often employ VEGFR TKI therapies in sequential manner. With use of ICB in the first-line setting, focus has shifted towards overcoming primary and adaptive mechanisms of treatment resistance.

For patients with non-clear cell histologies, no sub-type specific large-scale trial has defined therapy standards, and VEGFR TKI treatment with sunitinib remains the most frequently chosen agent given combined efficacy results in phase II trials conducted across all non-clear cell histologies (*41, 42*). Despite advancements in tumor subtyping at the molecular and genomic levels, treatment strategies that incorporate this data continue to lag. In patients with major papillary component or HLRCC (sporadic or syndromic), two treatment programs have been specifically developed. Combination bevacizumab and erlotinib have preliminarily shown an ORR 60% compared to 29% in HLRCC patients versus sporadic papillary tumors, respectively, with a significantly prolonged PFS (*43*), however final results regarding the efficacy of this regimen are pending. In a phase II trial, combination bevacizumab and everolimus also showed robust response rates in patients with major papillary component (ORR 43% versus 29% for all non-clear cell tumors), however does not identify genomic features of responding tumors (*44*). Retrospective analyses have shown that treatment naïve and refractory patients also have response to monotherapy immune checkpoint blockade (anti-PD-1/PD-L1) with varied ORR 10-20%, without any specific subtype / genomic alteration associated with response (*45, 46*).

Outcomes for patients with RMC are uniformly poor, with <5% of patients surviving greater than 36 months, and treatment guidelines have been proposed for patients based upon expert consensus (*47, 48*). Based upon a retrospective multi-center review, cytotoxic chemotherapy was shown to have an ORR of 29%, generally of short duration. The reported regimens in the report reflect commonly used therapeutic strategies for RMC and included carboplatin / paclitaxel, carboplatin / paclitaxel / bevacizumab, carboplatin / gemcitabine, and gemcitabine / doxorubicin. In the same multicenter study, over half of the patients were subsequently treated with a targeted agent (sunitinib, bevacizumab, pazopanib, sorafenib, everolimus, imatinib), and treatment had a median duration of 8

weeks with an ORR of 0% (*49*). This highlights a desperate need to develop new regimens for this unfortunate group of young RMC patients.

3.8 Combination PARPi and ICB Rationale

Combination PARPi with immune checkpoint blockade therapy may provide additive or synergistic effects based upon several rationales (*50*). PARPi induced DNA damage may increase overall tumor mutational burden (TMB) thereby increasing overall neoantigen repertoires for increased cytotoxic T-cell exposure through epitope diversity and enhanced immune stimulation. RCC has only modest TMB compared with other tumors which are traditionally immune sensitive (*51*), and mutational burden has been shown to lead to enhanced clinical benefits irrespective of PD-L1 status in other tumor models (*52, 53*). Moreover, PARPi induced DNA DS breaks inherently lead to accumulation of cytosolic DNA which in turn activates the STING (stimulator of interferon genes)/cGAS innate immune pathway for stimulation (*54*), and therefore PARPi achieves anti-tumor immune effects outside of synthetical lethal mechanisms. Interestingly, pre-clinical work has shown that PARPi increases PD-L1 expression, and blockade of PD-1/PD-L1 axis through PD-1 blockade may resensitize tumors to ICB therapy (*55*), leading to prolonged model survival compared with PARPi alone *in vivo* (*54*). PARPi treatment also leads to release of many pro-inflammatory cytokines like IFN-γ and TNF-α, thereby priming the microenvironment for enhanced immune effector responses in combination strategies.

Importantly, early trials have employed combination PARPi and ICB therapy without significant overlapping toxicities seen thus far in early signals. The proposed combination of talazoparib and avelumab is being investigated in other tumor models (NCT03330405), and other PARP + ICB combinations are being tested in many HR deficient (i.e. *BRCA* mutant) populations (NCT02734004, NCT02484404, NCT02953457). Interestingly, preliminary responses have been seen in unselected tumor models (*BRCA* mutant and wild-type) with combination approaches. A phase I trial of pamiparib (BGB-290), a selective PARP inhibitor with tisleizumab (anti-PD-1) has shown preliminary efficacy across multiple tumor types (NCT02660034), and in both *BRCA*-mutant and wild-type patients (*56*).

3.9 Talazoparib Pre-Clinical and Clinical Experience

Talazoparib / BMN-673 is a bioavailable, oral PARP1 and PARP2 inhibitor that blocks PARP enzyme activity and allows for persistent PARP trapping onto DNA, all of which lead to enhanced cytotoxicity via inadequate repair of DNA damage. Talazoparib was FDA approved in October 2018 for the treatment of adult patients with deleterious or suspected deleterious germline BRCA mutated, HER2 negative, locally advanced or metastatic breast cancers, tested with an FDA approved companion diagnostic designation.

Early phase data has shown that talazoparib pharmacokinetics remain linear with doses increased from 0.25 – 2 mg, and median time to maximum plasma concentration is 1-2 hours after each dose with a steady-state within 2-3 weeks. Talazoparib undergoes minimal hepatic metabolism and is mainly renally excreted. Pre-clinical work has also

shown that when compared to other PARP inhibitors including olaparib and rucaparib, talazoparib has a stronger potency for PARP inhibition and resultant cytotoxicity (*57*).

FDA approval was based on the EMBRACA study, a phase III, open-label, multi-center study (NCT01945775) which evaluated talazoparib 1 mg daily and physician's choice chemotherapy in patients with treatment refractory *BRCA*-mutant, locally advanced or metastatic breast cancer (*20*). Enrolled patients were treated until disease progression or unacceptable toxicity, and the median duration of study treatment was 6.1 months versus

3.9 months for talazoparib and physician's choice chemotherapy, respectively. The major efficacy outcome measure was PFS evaluated by RECIST v1.1 assessed by blinded independent central review. When compared to chemotherapy, talazoparib monotherapy showed a PFS of 7.6 months versus 5.6 months (HR 0.54, p<0.0001), ORR 50.2% versus 18.4%, and median duration of response of 6.5 months versus 3.9 months.

Dosing interruptions due to adverse reactions of any grade occurred in 65% of patients who received talazoparib, and dose reductions due any causes occurred in 53% of patients who received talazoparib versus 40% of patients on chemotherapy. Permanent discontinuation due to adverse reactions of talazoparib was only seen in 5.9% of patients with talazoparib. In <20% of patients treated with talazoparib on trial, following adverse reactions were seen including abdominal pain (19%), dizziness (17%), leukopenia (17%), dysgeusia (10%), dyspepsia (10%), stomatitis (8%), and lymphopenia (7%). Adverse reactions are outlined (Table 3).

Adverse Reactions (in ≥20% of Patients Receiving Talazoparib) in EMBRACA Adverse Reactions	**Talazoparib N=286 (%)**			**Chemotherapy N=126 (%)**		
	Grades 1-4	**Grade 3**	**Grade 4**	**Grades 1-4**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia	53	38	1	18	4	1
Neutropenia	35	18	3	43	20	16
Thrombocytopenia	27	11	4	7	2	0
Metabolism and nutrition disorders						
Decreased appetite	21	<1	0	22	1	0
Nervous system disorders						
Headache	33	2	0	22	1	0
Gastrointestinal disorders						
Nausea	49	<1	0	47	2	0
Vomiting	25	2	0	23	2	0
Diarrhea	22	1	0	26	6	0
Skin and subcutaneous tissue disorders						
Alopecia	25	0	0	28	0	0
General disorders and administration site conditions						
Fatigue	62	3	0	50	5	0

Table 3: Summary of >20% Adverse Reactions on EMBRACA Phase III Trial. The majority of non-hematologic events in talazoparib group were grade I in severity (Adapted from (*20*)).

3.10 Avelumab Pre-Clinical and Clinical Experience

Avelumab / MSB0010718C is a human IgG1 monoclonal antibody that blocks PD-L1 thereby competitively disrupting the immune checkpoint in T-cell regulation. Amongst other immune checkpoint blockers, avelumab is uniquely human IgG1 and therefore additionally is capable of antibody dependent cell mediated cytotoxicity due to its native Fc region (*58*).

In the early phase trial (JAVELIN, NCT01772004 (*59*)) pharmacokinetic analyses have shown that there remains a dose proportional exposure of avelumab from 3 mg/kg – 20 mg/kg, and population studies have shown no significant effects on clearance of avelumab from premedications or concomitant therapies like opiates or corticosteroids. Avelumab has a drug half-life of 95-99 hours at the 10 mg/kg and 20 mg/kg dose. Receptor target occupancy was >90% at 3-10 mg/kg doses. Anti-drug antibodies have been detected in minority of patients (4% in early phase trial). Primary excretion of avelumab remains intracellular lysosomal proteolytic degradation, with a terminal half-life of 65.1 days in patients receiving 10 mg/kg. Avelumab is not expected to interfere with small molecular drugs through p450 enzyme modulators or through absorption or elimination.

Avelumab gained FDA regulatory accelerated approval based on clinical response for patients with metastatic Merkel cell carcinoma (MCC) in March 2017. In the JAVELIN Merkel 200 trial (NCT02155647), an open-label single-arm multicenter study in patients with metastatic treatment refractory MCC, patients received avelumab 10 mg/kg every 2 weeks with an ORR of 32%, complete response (CR) of 11.4% and partial response (PR) of 21.6%. The duration of response was 2.8-23.3+ months, with 45% of patients sustaining a clinical response ≥12 months (*60*). Updated results from JAVELIN Merkel 200a Part B testing monotherapy avelumab in the first-line setting continue to show robust and durable responses (*61*). Multidisplinary review of avelumab for accelerated regulatory approval showed that simulated AUC for 10 mg/kg Q2 week dosing had similar overall drug variability for both body weight based and flat dosing schemes, and a flat dosing regimen should be acceptable. As such, the FDA-label for avelumab was updated in October 2018 for a recommended flat-dose schedule instead of traditional weight-based dosing. Recently launched clinical investigations have also incorporated this approach, notably the JAVELIN-PARP phase II clinical trial in BRCA/ATM mutant tumors (NCT03330405)(*62*), and other phase II combination treatments (i.e. NCT03704467).

In May 2017, avelumab received FDA accelerated approval for the use in locally advanced or metastatic urothelial carcinoma who have had disease progression during or following platinum-containing chemotherapy, and in patients with disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy. Results from the urothelial carcinoma cohort of the JAVELIN solid tumor trial showed a confirmed ORR of 16.1%, with a CR rate of 5.6% and PR rate of 10.6% with ≥6 months follow-up (*63*).

Recent early phase data from the JAVELIN phase I solid tumor renal cell carcinoma cohort of avelumab 10 mg/kg monotherapy every 2 weeks has shown monotherapy clinical activity in both the first-line and second-line settings (Table 4) (*64*). In JAVELIN Renal 101,

a phase III study combining avelumab and axitinib, a VEGFR TKI, compared to sunitinib, superior results were seen with combination therapy, including: ORR 51% versus 26% by IRC, improved PFS 13.8 months versus 8.4 months (HR 0.69, p=0.0001) (*65, 66*).

Treatment Line	Patient #	Follow-Up	TRAE (grade >3)	ORR	Duration of Response	mPFS	mOS
IL	62 patients	14.2 months (6-17)	12.9%	16.1% (8-27.7%)	10.4 (2.8-10.4)	8.3	NE
2L	20 patients	22.1 months (16-23)	5%	10% (1.2-31.7%)	NE (6.9-NE)	5.6 (2.3-8.2)	16.9 (8.3-NE)

Table 4: Avelumab Monotherapy in ccRCC. 1L: first-line 2L: second-line TRAE: treatment-related adverse events ORR: objective response rate mPFS: median progression-free survival mOS: median overall survival

Pooled safety data regarding monotherapy avelumab from the phase I JAVELIN solid tumor and phase II JAVELIN Merkel 200 clinical trial (1650 patients + 88 patients, respectively) has been reported (*67*). Grade ≥3 treatment related adverse events were seen in 177 patients (10.2%), with the most common being fatigue 1%, increased lipase 1%), infusion related reactions (0.6%), and nausea (0.6%). Immune related adverse events occurred at any grade in 14.2% of patients (247/1738), with the most common including endocrinopathies (6.1%) of which thyroid (5.6%) remained the most predominant, as well as rash (5.2%) of any grade. Grade ≥3 immune related adverse events occurred in 1.8% of patients only. Other clinical significantly, immune related adverse reactions occurring at an incidence of <1% of patients treated with avelumab have also included immune-mediated myositis, arthritis, pemphigoid, hypopituaritism, Guillan-Barre syndrome, and systemic inflammatory response.

3.11 Combination Talazoparib and Avelumab Combination Therapy

As avelumab is eliminated by proteolytic degradation, it is not expected to be affected by small molecule drugs, the cytochrome p450 enzyme system, or the absorption or elimination of other small molecule drugs. Therefore, expected drug-drug interactions with combination talazoparib and avelumab are low. Furthermore, there does not appear to be overlapping toxicities anticipated with this combination given with known individual safety profiles. Avelumab has been previously combined with axitinib for patients with advanced RCC with no unexpected safety signals in a large-scale randomized study (*65*). Reported treatment emergent events ≥3 in the combination were 71.2% versus 71.5% with sunitinib monotherapy.

Based on the above rationales, this clinical trial is testing the combination of talazoparib and avelumab in patients with metastatic renal cell carcinoma in two genomically defined populations. Based on the phase Ib portion of the JAVELIN PARP Medley (NCT03330405), in which patients were treated with 0.5 mg, 0.75 mg, and 1 mg daily talazoparib and 800 mg avelumab the recommended phase II dose (RP2D) was 1 mg

talazoparib for combination therapy. This RP2D was considered based upon a lower observed DLT rate than pre-specified rate per protocol (<0.33). No unexpected AEs were also seen with combination avelumab and talazoparib compared to the expected profiles of each individual agent, and the incidence and severity of AEs was generally consistent with previously observed rates for each individual agent and were generally manageable (Summary of Phase Ib Safety Data, Pfizer Internal Communication).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II, open-label, single institution clinical trial of combination talazoparib and avelumab in patients with metastatic RCC. This clinical trial will enroll two separate cohorts in parallel. The first cohort of patients will include *VHL*-deficiency and will enroll in a Simon two-stage manner (first stage=10 patients, second stage=19 patients, total=29 patients) to allow for early futility analysis and final efficacy analysis. The second cohort will enroll 15 patients with either *FH*- or *SDH*-deficiency or renal medullary carcinoma (RMC), and will enroll a total of 15 patients continually given disease rarity for each of these three entities. Given the uniformly aggressive nature of RMC, typically with rapidly progressive clinical picture without standard treatment options following failure of first-line chemotherapy, and considering the fact that SMARCB1 (INI1) is lost in nearly all patients, we will not require IHC/NGS testing for RMC patients as part of study eligibility.

4.2 Intervention

Combination talazoparib and avelumab will be administered in 28-day cycles until disease progression or unacceptable toxicity. All treatments will be given in the outpatient clinic. Avelumab will be administered as a 1-hour intravenous infusion every 2 weeks on days 1, 15 of each 28-day cycle, at a flat dose of 800 mg. Premedication with acetaminophen and diphenhydramine will be included for all patients to minimize risk for infusion-reactions as specified in Section 5.3. Talazoparib will be self-administered orally at 1 mg daily on a continuous schedule. All study medications will be supplied by Pfizer.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Talazoparib Drug Information and Storage

Commercial supply of Talazoparib / BMN-673 will be acceptable for this protocol, and drug will be supplied by trial sponsor Pfizer. Drug will be supplied in a dosing container which will contain sufficient drug for each treatment period including overage. Talazoparib will be stored at room temperatures (15-30ºC, 59-86ºF) or per the approved label. Research staff will inform patients on the proper storage requirements for the take home investigational drug. Further information regarding talazoparib handling is listed in the investigational brochure. Any excursions from the product label storage conditions will be reported upon discovery. Deviations from the storage requirements should be documented and reported. Once an excursion is identified, the investigational product

must be quarantined and not used until Pfizer provides permission to use the investigational product.

Talazoparib is self-administered orally once daily on a continuous schedule during days 1-28 of the treatment cycle. Talazoparib should be at the same time, and if a dose is missed, it may be taken up to 12 hours after scheduled time. Patients should not take more than one dose within a 24-hour period, and if any doses are missed in the cycle, they will not be made up and should be recorded as missing in the patient's diary. The reason for the missed dose should be recorded in the diary for study personnel to review. The patient is then instructed to resume subsequent doses the next day as prescribed.

Patients are to self-administer talazoparib orally with or without food. Capsules should be swallowed whole with a glass of water without chewing, dissolving or opening prior to swallowing. Talazoparib can be taken with a light meal/snack, and then should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs after talazoparib is swallowed, the dose itself should only be replaced if intact tablets are seen and counted.

Patients are not to exceed the prescribed dose at any time. The use of study medication in doses exceeding that specified in this protocol will be considered an overdose. There are no known antidotes for talazoparib in the event of an overdose, and treatment for adverse events should be aimed at underlying adverse symptoms.

6.1 Avelumab Drug Information and Storage

Commercial supply Avelumab / MSB0010718C will be acceptable for this protocol, and drug will be supplied by Pfizer. Drug will be supplied as a clear, colorless, non-pyrogenic solution, packaged in a type I glass vial containing 10 ml of solution with a rubber stopper and aluminum overseal and flip off cap. Each single use vial of avelumab contains a sufficient amount of product to ensure an extractable volume of 10 ml (200 mg) at concentration of 20 mg/Ml, formulated with a preservative-free acetate buffered solution at pH 5.2 in the presence of polysorbate 20 and mannitol. Avelumab solutions must be prepared in 0.9% sodium chloride (normal saline), with final concentration of avelumab in the infusion solutions between 0.15 mg/mL to 8 mg/mL. Total volume of final prepared solution must be 250 mL. The parenteral investigational drug products must be inspected visually for particulate matter.

Avelumab must be stored in a refrigerator, at 2-8ºC, 36-46ºF. It is not frozen and must be protected from light. It cannot be shaken vigorously. The solution itself must be allowed to reach room temperature for a minimum of 30 minutes prior to dose preparation. The immediate administration of a prepared solution kept at room temperature is preferred. Further information regarding avelumab storage and preparation is provided in the investigational brochure.

Avelumab will be provided to each patient in the outpatient chemotherapy administration suite and will be provided on cycle day 1 and day 15 (every 2 weeks). Doses may be given

within a 72-hour period per visit window (Schedule of Activities), and if any doses are missed in the cycle, they will not be made up and should be recorded as missing. Avelumab will be administered with a pre-medication as per below (Section 5.3).

6.1 Avelumab Premedication

Avelumab must be infused with premedication to mitigate the rate of infusion-related reactions. Premedication will include antihistamine and acetaminophen 30-60 minutes prior to the first 4 infusions. Premedication should be then administered for subsequent avelumab infusion based upon clinical judgement and presence/severity of prior infusion reactions. Availability for immediate access to intensive care unit or equivalent environment for treatment of anaphylaxis is required. This should include access to steroids (i.e. dexamethasone), epinephrine (i.e. 1:1000 dilution), allergy medications (IV histamines), bronchodilators or equivalents, as well as oxygen. Following the first four infusions of avelumab, patients should be observed for at least 60 minutes for potential infusion related complications and reactions. Provided no infusion reactions are seen this observation period is not required beyond dose #4. If a hypersensitivity reaction occurs, the patient should be treated according to the best available medical practice with consideration for treatment modification (Table 5).

Symptoms of hypersensitivity reactions may include, but are not limited to, fevers, chills, hypotension, flushing, dyspnea, wheezing, back pain, abdominal pain, urticaria. Patients should be instructed to immediately report to the Investigator any delayed reactions that occur after clinic. Management of infusion related reactions are listed below, and in Appendix 3.

NCI CTCAE Severity Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening. • Next scheduled infusion can be re-attempted at original rate, per treating investigator's discretion.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume avelumab infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening • Next scheduled infusion should be initiated at 50% of original rate. Added premedication should be considered.

Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the patient. • Patients must be withdrawn immediately from avelumab treatment and should not receive any further avelumab treatment.

Table 5: Avelumab Infusion Reaction Algorithm. For each NCI CTCAE grade, a treatment modification instruction should be followed.

If the infusion rate of avelumab has been decreased by 50% due to an infusion reaction, it should remain at the decreased infusion for the next scheduled dose. If no infusion reactions were observed during that next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.

If, in the event of a Grade 2 infusion related reaction that does not improve or worsens after implementation of the modifications indicated above (including reducing the infusion rate by 50%), systemic corticosteroids should be considered, per treating physician's discretion and with discussion with the PI. At the next dose, the treating physician should consider addition of H2 blocker antihistamines (i.e. famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic corticosteroids up to the equivalent of 10 mg prednisone could be considered for recurrent grade 1-2 reactions despite premedication with above medications.

6.1 Treatment Interruptions / Delays

Talazoparib may be maximally interrupted for 28 consecutive days. Avelumab may be maximally interrupted for 42 consecutive days. Should treatment toxicities warrant longer treatment interruptions than these, the respective agent should be discontinued permanently.

If a treatment-related adverse event is clearly attributable to one, not both, of the two investigational agents and triggers a treatment interruption per protocol guidelines, the other agent may be continued at the treating investigator's discretion. In the case of permanent discontinuation of either agent despite the absence of disease progression, the other drug may be continued as monotherapy, if tolerable.

For the therapy cycle, it will be acceptable to have therapy delivered within a 72-hour window before and after the protocol related date. The exception for this 72-hour window rule will be if regularly scheduled treatment dates occur on Fridays, as the window will include Tuesday (day -3), and Tuesday (D+4).

For each 28-day treatment cycle, the patient may be permitted to have a new cycle delayed for up to +7 days without being considered a protocol deviation.

6.1 Drug Accountability

The study team will maintain adequate documentation regarding the receipt, use, loss and other dispositions of all investigational drug supplies. All the investigational products should be accounted for using a drug accountability form/record. Unused talazoparib must be returned to the investigator or study team personnel by each patient on Day 1 of every cycle and at the end of the clinical trial participation.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Biopsy proven, histological confirmed renal cell carcinoma (RCC) or renal medullary carcinoma (RMC). Patients with surgery and biopsy at outside institutions will be eligible for this protocol once archival material is reviewed and the above diagnosis confirmed by genitourinary pathology review at Memorial Sloan Kettering Cancer Center (MSKCC).

2. **Cohort 1:**
   - **a.** Presence of *VHL* alteration by next-generation sequencing (NGS) with a state- approved assay
   - **b.** Patients must have radiographic evidence of disease progression after treatment with at least one prior PD-1 or PD-L1 agent and one prior VEGF inhibitor
   - **c.** Maximum 3 prior lines of therapy

3. Cohort 2:
   - **a.** For FH/SDH patients: FH- or SDH- expression-loss by immunohistochemistry (IHC) or alteration (somatic or germline) in *FH* or *SDH* per NGS with a state-approved assay
   - **b.** For Renal Medullary Carcinoma (RMC) patients: histologic confirmation of RMC (no IHC/NGS criteria required)
   - **c.** At least one prior line of therapy:
     - **i.** For FH/SDH patients: Patients must have radiographic evidence of disease progression after treatment with at least one prior line of therapy (one prior PD-1/PD-L1 and/or VEGF inhibitor).
     - **ii.** For Renal Medullary Carcinoma (RMC) patients: prior radiographic evidence of disease progression on/after at least one line of chemotherapy (e.g. carboplatin / paclitaxel, carboplatin / paclitaxel / bevacizumab, carboplatin / gemcitabine, and gemcitabine / doxorubicin).
   - **d.** No maximum lines of therapy

Both Cohorts 1 & 2:

4. Adequate Hematologic Function
   (1) Absolute Neutrophil Count ≥ 1.5 x 10^9 / L
   (2) Platelet Count ≥ 100 x 10^9 / L
   (3) Hemoglobin ≥ 9 g/dL
   (4) No transfusion of packed red blood cells or platelets within 21 days of Cycle 1 Day 1
5. Adequate Renal Function ≥ 30 ml/min according to Cockcroft-Gault Equation
   (1) Patients with moderate renal impairment (creatinine clearance 30-59 by Cockcroft-Gault Equation) will start with a reduced dose of talazoparib.
6. Adequate Hepatic Function including:
   (1) Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
   (2) AST ≤ 3 x upper limit of normal (ULN) without liver metastasis
   (3) ALT ≤ 3 x upper limit of normal (ULN) without liver metastasis
   (4) AST or ALT ≤ 5 x upper limit of normal (ULN) for patients with liver metastasis
   (5) Patients with known Gilbert's syndrome may be included if total bilirubin ≤ x 3 ULN
7. Eastern Cooperative Group (ECOG) Performance Status 0-2.
8. Patients must have measurable disease by RECIST v1.1. At least one measurable lesion should not have been previously irradiated.
9. Women of childbearing potential must have negative serum pregnancy testing at screening. All women will be considered childbearing potential unless meeting criteria including:
   (1) Achieved post-menopausal status as defined by cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have follicular stimulation hormone showing postmenopausal state. Women who have been amenorrhoeic for ≥12 months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anorexia, low body weight, ovarian suppression, anti-estrogen therapy or other medically inducible reasons.
   (2) Documented hysterectomy or bilateral oophorectomy surgery
   (3) Medically confirmed ovarian failure
   (4) Sexually active participants and their partners must agree to use medically accepted methods of contraception (i.e. barrier methods including condoms, female condom, or diaphragm with spermicidal gel) during the study and for 7 months after the last dose of the study treatment for females, and 4 months for males.
10. Recovery of baseline CTCAE v5.0 grade ≤1 toxicities related to prior study treatments unless adverse events are clinically non-significant and/or stable on supportive therapy if needed.
11. Patients must be willing and able to comply with trial protocol. This includes adhering to the treatment plan, scheduled visits, laboratory and other study procedures.

6.2 Subject Exclusion Criteria

1. Patients < 18 years old

2. Patients who are pregnant or breast-feeding. Fertile patients who are unwilling or unable to use two methods of contraception (at least one of which considered highly effective) for duration of study and after 7 months after last dose of study treatment for female, and 4 months for males.
3. Patients who had prior immune checkpoint blockade therapy (either anti-PD-1, anti-PD-L1 and/or anti-CTLA-4) discontinued due to development of an immune related adverse event.
4. Prior diagnosis of myelodysplastic syndrome (MDS) or diagnosis of other malignancy that requires anti-cancer directed therapy within the last 24 months. Exclusions include those cancers that are considered cured by local therapy (i.e. Basal cell carcinoma, squamous cell carcinoma, ducal carcinoma in situ of breast, bladder of cervix) or other cancers that have low malignant potential and do not require systemic therapy (i.e. Gleason-grade <6 prostate adenocarcinoma, borderline ovarian malignancy / low malignant potential).
5. Prior treatment with talazoparib or other agents that target PARP
6. Treatment with anti-cancer therapies within 21 days or five half-lives, whichever shorter, of start date, including monoclonal antibody, cytotoxic therapy, or another investigational agent. There is no specific time window between last PD-1/PD-L1 therapy and start date of new therapy on protocol.
7. Significant vascular disease (i.e. aortic aneurysm requiring surgical repair, recent arterial thrombosis) within 6 months prior to first dose of therapy.
8. Evidence of bleeding diathesis or significant unexplained coagulopathy (i.e. absent of anticoagulation)
9. Clinical signs or symptoms of gastrointestinal obstruction requirement parenteral hydration, parenteral nutrition, or feeding tube.
10. Uncontrolled effusion management (pleural effusion, pericardial effusion, or ascites) which requires recurrent drainage procedures.
11. Patients treated with systemic immunosuppressants; except for
    a) chronic physiologic replacement of ≤ 10mg prednisone (or equivalent) for treatment of adrenal insufficiency; Steroids required for pre-medication reactions
    b) Local steroid use is permitted (e.g. intranasal, topical, inhaled, or local steroid injection, i.e. intra-articular)
12. Patients with autoimmune disease that may worsen during immune checkpoint blockade therapy are excluded. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requirement immunosuppressive treatment as above are eligible.
13. Prior organ transplantation including allogeneic stem cell transplant.
14. No active infection requiring parenteral antibiotic therapy.
15. Prior diagnosis of HIV/AIDS
16. History of either positive HCV RNA viral load or anti-HCV antibody screening detectable; HBV infection with HBV surface antigen detection and/or positive HBV DNA viral load.

17. Known hypersensitivity to talazoparib or avelumab, or any component in formulations. Patients with known hypersensitivity to monoclonal antibodies (Grade ≥3 by CTCAE v5.0)
18. Live vaccination within 4 weeks of first dose of therapy. All vaccines except inactivated are prohibited while on study.
19. Severe acute or chronic medical conditions which may significantly increase the risk of study participants, per treating investigator's discretion
20. Radiation therapy to any site (including bone) <2 weeks prior to the first dose of therapy. Patients with clinically relevant ongoing complications from prior radiation therapy, per investigators' assessment, are not eligible.
21. Symptomatic brain metastasis or leptomeningeal disease requiring steroid use. Patients are eligible if they neurologically stable for 4 weeks, and have completed radiation therapy or surgery, and recovered from side effects. Patients must have discontinued steroid therapy for at least 2 weeks prior to first dose of study treatment.
22. Current or anticipated use of potent P-gp inhibitors within 7 days prior to randomization or anticipated use during the study. Please see Appendix 5 for a list of potent P-gp inhibitors.
23. Inability to swallow capsules, known intolerance to talazoparib or its excipients, known malabsorption syndrome, or other conditions which impair intestinal absorption.
24. Investigator site staff members directly involved in study conduct, including but not limited to their family members, or patients who are Pfizer members, including their family members, who are directly involved in study conduct.

6.3 Lifestyle Requirements

The teratogenic risk of combination talazoparib and avelumab remains unknown. Talazoparib has been associated with teratogenic risk. Therefore, all fertile male patients and female patients who are of childbearing potential, and who remain sexually active during this study and who are at risk for pregnancy must agree for 2 methods of contraception (one which is considered highly effective), for at least 7 months after last dose of study treatment for women, and for at least 4 months after last dose of study treatment for men.

Study team personnel including investigators and clinical nursing staff should confirm that the patient and their partner have selected 2 appropriate methods of contraception from the list of contraceptive methods (as listed below). The study team will confirm that the patient has received informed consent regarding proper use. Continued confirmation of contraceptive use will be obtained during the study protocol at time points outlined, with documentation of affirmation.

Highly effective contraceptive methods include, but not limited to:

1. Established hormonal methods of contraception associated with ovulation inhibition (i.e. oral, inserted, injected or implanted), provided that the patient

or male patient's partner remains on same treatment throughout the entire study period.

2. Intrauterine device
3. Male sterilization with absence of sperm in post vasectomy ejaculate
4. Bilateral tubal ligation, bilateral salpingectomy or bilateral tubal occlusive procedure.
5. Female partner of male patient who meets criteria for non-childbearing potential as defined above, including:
   a. Medically confirmed ovarian failure
   b. Hysterectomy and/or bilateral oophorectomy
   c. Post-menopausal state as defined as a cessation of regular menses >12 months with no alternative pathologic or physiologic cause, with serum follicular stimulating hormone within reference range for postmenopausal women by laboratory.
6. All sexually active male patients must agree to prevent potential transfer or exposure of study agents through ejaculate by using a condom consistently and correctly. Condom use must begin at the first dose of investigational product, and for at least 30 days after avelumab or after at least 4 months after last dose of talazoparib, whichever is later.

7.0 RECRUITMENT PLAN

Patients will be recruited in the outpatient genitourinary medical oncology service clinics at Memorial Sloan Kettering Cancer Center (MSKCC). Investigators listed on this protocol will screen patients for eligibility for trial participation. Men and women of all ethnic groups are eligible for participation. Alternative treatment options, particularly FDA approved regimens will be discussed with each patients, and questions will be answered by the treating investigator before written consent is obtained.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

Pre-treatment evaluation to be completed ≤30 days prior to study treatment day 1.

1. History and Physical Examination
2. Vital Signs
3. Eastern Cooperative Group (ECOG) Performance Score
4. Toxicity Assessment via CTCAE v5.0
5. Assessment of concomitant medications and treatment
6. 12-lead electrocardiogram
7. Optional pre-treatment biopsy
8. Radiographic tumor assessment of chest, abdomen, or pelvis
9. Radiographic brain imaging
10. Bone scan if clinically indicated
11. Verification of tumor alteration status by state-approved NGS assay (MSK IMPACT or other)
12. Confirmation of tissue availability:
    (1) Availability of archival tissue must be confirmed prior to study initiation, but specimens do not have to be physically received or processed for determination of eligibility; 20 unstained slides should be requested, but there is no minimum slide requirement.
13. Peripheral Blood Tests including:
    (1) Complete blood count with differential (including at minimum neutrophils, basophils, eosinophils, lymphocytes, monocytes, hematocrit, platelet count, hemoglobin, RBC count)
    (2) Comprehensive Metabolic Profile (including alkaline phosphatase, AST, ALT, Total bilirubin, total protein, albumin, sodium, potassium, chloride, carbon dioxide, bicarbonate, calcium, BUN, creatinine, amylase, lipase, glucose)
    (3) Lactate Dehydrogenase
    (4) Serum Pregnancy Testing for women of childbearing potential
    (5) Thyroid Function Testing: TSH, free T4, free T3
    (6) Urinalysis; urine protein / creatinine ratio

(7) Screening for hepatitis B: HBV surface antigen, HBV core antibody, with HBV PCR performed reflexively if abnormal results
(8) Screening for hepatitis C: anti-HCV antibody and HCV RNA PCR performed reflexively if abnormal results

9.0 TREATMENT/INTERVENTION PLAN

Talazoparib and avelumab will be initiated concurrently on Cycle 1 Day 1 and both will be continued until confirmed disease progression (except where treatment is allowed beyond progression; refer to section 10.6 for further information), patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first.

If talazoparib is held for > 28 consecutive days, it should be permanently discontinued. If avelumab is held for > 42 consecutive days, it should be permanently discontinued. Should the treating investigator determine that exceptional circumstances apply and that it would be clinically beneficial for the patient to re-initiate therapy after a longer treatment break, re-initiation must be discussed with and approved by the study PI. In the event that treatment-related toxicity is clearly attributable to only one of drugs, the other can be continued while the first is being held.

9.1 Talazoparib Administration

Talazoparib / BMN-673 will be provided to study participants in capsules for oral self-administration. The 0.25 mg (opaque, white) and 1 mg (opaque, pale pink) capsules are supplied in separate bottles and labeled according to regulatory requirements. Talazoparib will be packaged in induction sealed, high density polyethylene bottles with child resistant caps with 30 capsules of a single strength per bottle.

On Day 1 of each treatment cycle, talazoparib will be dispensed by the clinical team. The patient and/or caregiver should be instructed on how to maintain the product in the bottle during treatment cycle, keep investigational products away from children, and will be instructed to return the bottle to the site on Day 1 visit of the subsequent treatment cycle.

Talazoparib is a cytotoxic agent, and therefore precautions regarding the appropriate secure storage and handling must be used. To minimize undue exposure to study personnel, dispensing, handling and safe disposal of talazoparib should only be done by qualified personnel at MSKCC. Patients should be advised that talazoparib is an oral anti-cancer therapy and therefore handling of the agent should be done always be used with gloves.

9.2 Avelumab Administration

Avelumab / MSB0010718C will be provided to the pharmacy as a sterile, clear, colorless solution that can be prepared for intravenous administration. Each participant will receive a dose of 800 mg intravenously every 14 days. Therefore, 4 vials of avelumab drug product will then be diluted with 0.9% saline solution. Detailed information regarding instructions

for avelumab preparation with dilution and subsequent administration is available in the Investigational Brochure and above. Any spills that occur during administration should be cleaned by facility's standard cleanup procedures for biological products.

9.3 Talazoparib and Avelumab Combination Administration

For each 28-day cycle, combination talazoparib and avelumab will be administered on Days 1 and15. For Cycle 1, Day 1, medications will be administered per the following order:

1. All required tests and assessments will be performed prior to medication dosing.
2. Avelumab premedication and talazoparib will be administered to the patient in any order chosen by the study team.
3. Avelumab infusion will start within 30-60 minutes after the avelumab premedication was administered.

For subsequent cycles where patients are administered both study agents, patients may take talazoparib prior to being seen by the clinical team and are encouraged to continue the same dosing order as above.

9.4 Medication Compliance

All doses of avelumab will be administered at MSKCC by trained medical staff. All start and stop times of the avelumab infusion, as well as dosing information including infusion time, volume administered, interruption to infusion and/or changes in rate will be documented in patient medical records. Vials of avelumab that are assigned and prepared for patients will be recorded in the pharmacy records, and these records will be made available to the Sponsor representatives to verify medication compliance.

All doses of talazoparib will be given to the patient at the start of each cycle, and all patients will be required to return all unused talazoparib at the start of the subsequent cycle. The number of capsules returned by the patient will be counted, documented, and recorded by investigational personnel and reconciled with the patient's dosing diary to support talazoparib accountability. Study personnel should make reasonable efforts to obtain study drug packaging and unused capsules from those patients who do not routinely return them at the study site visit, and unreturned capsules will be considered to have been taken unless otherwise reported by the patient.

A medication dosing diary will be given to the patient to aid in patient compliance and dosing instructions. The diary will be maintained by the patient and will include entry items for the patients to include information regarding taken, missed, or changed talazoparib doses. Patients will be required to return this completed patient dosing diary on Day 1 of every new cycle for timely review by the study personnel during clinical visit. During the medical visit, review of this diary as well as discussion regarding missed doses or compliance issues will be done to ensure medication compliance and accurate data entry. During this clinic visits in which patients present for avelumab (day 1 and day 15), patients

are instructed to delay talazoparib dose administration so that it is performed in clinic, witnessed by study personnel.

Treatment compliance will ultimately be reported as a percentage and will be defined by the number of capsules taken during study treatment / number of expected capsules taken, multiplied by 100.

9.5 Talazoparib Dose Modifications

Talazoparib dose modifications can be implemented to help manage toxicities encountered during treatment. Dose reduction will be done per dosing level scheme listed below (Table 6). All patients will start on 1 mg daily (RP2D, Pfizer internal communication) and be allowed 1 dose level reduction at a time depending on the starting dose, type and severity of the toxicity. **For patients with known moderate renal impairment (Creatinine Clearance=30-59 mL/min by Cockcroft-Gault Equation) at treatment start or if renal impairment unrelated to study drug develops during the study, talazoparib should be reduced by one dose level (e.g. starting dose 0.75 mg daily). If the renal function improves, per investigator judgement this dose can then be increased.**

Patients experiencing dose-limiting toxicities from talazoparib will be dose-reduced to the next lower level. In the event of planned dose reduction, patients should hold study treatment for at least 48 hours prior to re-initiation of dose reduced therapy. Such dose reductions may be performed prior to scheduled initiation of subsequent study cycles, i.e. in the course of a treatment cycle. In such cases lower-strength capsules will be dispensed mid-cycle, rather than delaying re-initiation of therapy at lower dose. Left-over capsules at the prior strength will be returned to the study team at the next scheduled Day 1 clinic visit. Once the talazoparib dose has been reduced to a dose level because of toxicity for a patient, all subsequent cycles should be administered at that dose level unless further reduction is required. Subsequent re-escalation to prior dose levels will not be permitted. Patients who are unable to tolerate 0.25 mg (dose level -3) daily will be permanently discontinued from the talazoparib but may be considered for continuation of single-agent avelumab.

If talazoparib is held for >28 consecutive days, it should be permanently discontinued. Should the treating investigator determine that exceptional circumstances apply and that it would be clinically beneficial for the patient to re-initiate therapy after a longer treatment break, then re-initiation must be discussed with and approved by the study PI. If talazoparib is discontinued, patients may continue avelumab.

Dose Level	Talazoparib Dose
Dose Level 0	1 mg daily
Dose Level -1	0.75 mg daily
Dose Level -2	0.5 mg
Dose Level -3	0.25 mg daily

Table 6: Talazoparib Dose Levels for Cohorts 1 and 2.

9.6 Avelumab Dose Modifications

There will be no dose modification for avelumab during the duration of this study. If the treatment cannot be delivered due to an immune related adverse event, then avelumab will be placed on hold. It is acceptable for the patient to continue avelumab with resolution of ≤1 grade I immune related adverse event, and if patient is ≤10 mg prednisone (or equivalent) as deemed by investigator.

If avelumab is held for > 42 consecutive days, it should be permanently discontinued. Should the treating investigator determine that exceptional circumstances apply and that it would be clinically beneficial for the patient to re-initiate therapy after a longer treatment break, then re-initiation must be discussed with and approved by the study PI. If avelumab is discontinued, patient may continue talazoparib.

9.7 Concomitant Medications

Concomitant treatments are considered necessary for patients' well-being (anti-emetics, analgesics etc.) and may be given at the discretion of the investigator. All concomitant medications including herbal supplements, and supportive medications will be recorded in medical record from screening visit to 90 days after last dose of therapy. If after study treatment has concluded and patient had started new anti-cancer therapy, then further details regarding medications will be recorded until start of new anti-cancer therapy.

Allowed Therapy

1. Anti-emetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice as indicated. All patients who experience diarrhea should be advised to drink liberal quantities of liquids and if sufficient oral intake is not feasible, intravenous infusion of fluid and/or electrolytes should be performed.
2. Bisphosphonates or RANK-L inhibitors may be used to control bone loss if started prior to trial initiation or for hypercalcemia treatment if the benefit outweighs risk per investigator's discretion. As osteonecrosis of the jaw has been reported in those patients treated with bisphosphonate therapy, oral examination and serial examination during study is advised in those patients on bisphosphonate therapy.
3. Anticoagulation is allowed if the patient can be provided safely and effectively. This includes:
   (1) Use of low molecular weight heparin (LMWH) or direct oral anti coagulants (DOAC) such as rivaroxaban or apixaban is permitted provided the patient has no evidence of untreated brain metastases and has had no complications from thromboembolic event on the anticoagulation regimen within 14 days of starting study therapy.
   (2) All anticoagulants must be managed with accepted clinical guidelines. This includes standard patient education regarding medication compliance and administration, potential adverse drug reactions, monitoring of laboratory parameters (i.e. PT/INR/PTT/anti-Xa level), dose adjustments per standard

practice (i.e. dose adjustments for renal insufficiency), with consideration of referral to benign hematology for continued follow up and monitoring.

(3) Immunosuppressive drugs are permitted if initiated for management of treatment-related adverse events and in accordance with adverse event management recommendations in this protocol (See Section 11). Systemic corticosteroids, if indicated for management of cancer-related complications (e.g. with palliative radiation) are permitted. Depending on dosage (≤ vs. > 10mg prednisone daily or equivalent), administration of immunosuppressants may require avelumab treatment delays (See Section 11).

4. Caution and monitoring for potential increased adverse reactions should be used upon concomitant use of the following transporter inhibitors with talazoparib: atorvastatin, azithromycin, conivaptan, curcumin, cyclosporine, diltiazem, diosmin, eliglustat, elacridar [GF120918], eltrombopag, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract.

Prohibited Therapy

1. Any other anti-cancer therapy (chemotherapy, biological therapy, immunotherapy, vitamins used as cancer therapies) other than talazoparib and avelumab.
2. Any other investigational agents other than talazoparib or avelumab for anti-cancer or non-cancer related therapy.
3. Immunosuppressive drugs while on avelumab treatment other than indicated as above. Patients who have permanently discontinued avelumab for any reason and remain on study for talazoparib monotherapy are permitted to receive immunosuppressive drugs.
4. Potent P-gp inhibitors: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar, and verapamil) while on talazoparib treatment (see Appendix 5).
5. EPO stimulating agents: i.e. erythropoietin alpha, darbepoetin alfa,
6. TPO stimulating agents: i.e. romiplostim, eltrombopag, thrombopoietin

9.8 Concomitant Surgery

As the appropriate timing between surgery and administration of investigational agents is unknown, appropriate intervals must be taken to minimize the risk of impaired wound healing and bleeding. Therefore, investigational products should be temporarily on hold in the case of surgical procedure and be reinitiated on clinical assessment of satisfactory surgery recovery. The timing of such treatment interruption will be per treating investigator's discretion. Surgical removal of target lesions should prompt permanent discontinuation of study treatment.

9.9 Concomitant Radiation

Palliative radiation to non-target lesions may be administered in the setting of painful bony lesions and other sites as considered medically necessary per investigator. Sites that are to be irradiated must be present at the time of prior screening tumor assessment, and the investigator must be clear that the requirement for palliative radiation is not truly indicative of disease progression. Prior to radiation therapy, attempts should be made to truly rule out disease progression in the event there is localized pain. Investigational agents should be held during the duration of palliative radiotherapy and can be restarted upon satisfactory recovery for any radiotherapy related toxicities, but no sooner than 48 hours post-radiotherapy. Radiation of target lesions or radiotherapy prompted by local growth of metastatic disease are not permitted.

9.10 Hypercalcemia Management

Bisphosphonate or denosumab therapy can be administered as per loc al clinical practice. The need to start or escalate bisphosphonate or denosumab therapy for the management of malignant hypercalcemia during investigational drug treatment for those patients >2 weeks on investigational drug products may be considered a symptom of disease progression. As such, radiographic reassessment of disease extent should be considered if there is suspicion of disease progression.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Screening

All screening activities must be completed ≤28 days prior to study enrollment.
Procedures during screening are detailed under the Schedule of Activities (See Section 10.7).

10.2 Treatment Period

All activities during treatment period have been detailed under the Schedule of Activities (See Section 10.7). During times where multiple tests or procedures are scheduled during the same time point, the following priority should be assigned and adhered to in this order:

1. Vital Signs should be obtained prior to clinical safety laboratory testing but may be performed before or after ECG.
2. Clinical Laboratory Testing
3. All other study related procedures should be performed as close to scheduled times but may be obtained before or after blood specimen collection unless sampling is determined to impact results.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. If it is not feasible for the patient to perform the test, the investigator should make all necessary efforts to ensure the safety and well-being of the patient. When the protocol-related test cannot be performed, the investigator should document the reason for this and any corrective or preventative action to ensure that

normal processes are adhered to in the future for that patient. The study team should be informed of these incidents in a timely manner.

10.3 Safety Assessments

Safety assessments will include, but are not limited to, collection of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination, 12-lead electrocardiogram (ECG), laboratory assessments, pregnancy tests, and verification of concomitant medication and treatments. Adverse events will include the type, incidence, severity (as graded by NCI CTCAE v5.0), timing, seriousness and relatedness.

All patients should undergo height and weight (height will be measured at screening only), assessment for ECOG performance status, vital signs, and physical examination (full physical examination at screening, focused physical exam as indicated during follow-ups) prior to study treatment administration.

All patients will require a baseline ECG, and on-treatment ECGs should be performed as clinically indicated. Clinically significant findings on subsequent ECGs should be recorded as adverse events and best practice management should be followed including consideration of referral to cardiology for further evaluation and/or management.

Safety monitoring with hematologic and blood chemistry labs will be drawn at the time points as described in the Schedule of Activities (see Section 10.7). The required safety testing should be reviewed prior to study drug administration on Days 1 and 15 of each treatment cycle. Blood chemistry and hematologic assessment must be performed at baseline, prior to each avelumab dose, end of treatment visit, and 30 days post-treatment for safety follow up. For female patients of childbearing potential, urine pregnancy testing must be performed at baseline and at least every month during treatment. Thyroid function testing (Free T4, Free T3, TSH) must be performed at baseline, and at least every 4 weeks during treatment, and at the end of treatment visit or 30 days post-treatment in safety follow up (if not performed within 8 weeks of study treatment end).

Safety Lab Monitoring During Treatment	**Lab Parameters**
Hematology	WBC with differential, hemoglobin, hematocrit, Platelets, Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils

Chemistry	AST, ALT, Alkaline Phosphatase, Sodium, Potassium, Chloride, Total Calcium, Total Bilirubin, Urea/BUN, Creatinine, Glucose (non-fasted), Albumin, Total protein (screening), amylase (screening), Lipase (screening), LDH (screening)
Thyroid Function Testing	TSH, Free T4, Free T3
Urinalysis	Urine dipstick for urine protein – if positive, collect microscopic reflex testing. Urine dipstick for blood – if positive, collect microscopic reflex testing.
Pregnancy Testing	For female patients of childbearing potential, serum testing with a sensitivity of at least 25 mIU/mL.

Table 7: Lab Monitoring During Therapy. Abbreviations: WBC=white blood cell; ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, LDH=lactate dehydrogenase, TSH=thyroid stimulating hormone, T4=thyroxine, T3=triiodothyronine

10.4 Pregnancy/Contraception Safety Monitoring for Female Patients of Childbearing Potential

All pregnancy tests in this study must have a sensitivity of at least 25 mIU/mL human chorionic gonadotropin (hCG) and must be performed by a certified laboratory. For those female patients enrolled who are of childbearing potential, 2 negative pregnancy tests are required before receiving study treatment. These two tests will include negative pregnancy test during the screening period, and an additional negative pregnancy test at baseline on Cycle 1 Day 1 prior to receiving study treatment.

Following the negative pregnancy tests obtained at screening for trial enrollment, appropriate contraception must be commenced if sexually active. Pregnancy tests will then be required at baseline and will be repeated on Day 1 of every treatment cycle prior to dosing either study drug during active treatment period, and again at the End of Treatment visit to confirm that the patient has not become pregnant during the study period. Pregnancy tests will also be done during the study treatment if there is suspicion for pregnancy and may be requested by institutional review board (IRB)/ethics committees. In the case of a confirmed positive pregnancy test, the patient will be immediately withdrawn from the study treatment but may remain the study for follow-up purposes only (short term follow-up and long-term follow-up).

For female patients who are of childbearing potential and male patients capable for fathering children, affirmation that they meet criteria for the correct use of two selected methods of contraception must be obtained. The investigator or study personnel should discuss with the patient the need for contraceptive use consistently. In addition, patients will be instructed by the study personnel to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or patient's partner.

10.5 Disease Response Evaluation During Treatment

Tumor assessments will include all previously known disease sites. At screening, all patients will undergo cross-sectional imaging with CT chest/abdomen/pelvis with contrast if able, or non-contrast CT chest with paired MRI of abdomen/pelvis with contrast if patients are unable to receive CT contrast. Patients who have contraindications to MRI imaging but are not deemed candidates to receive iodine-based contrast will proceed with CT chest/abdomen/pelvis without IV contrast.

All patients will also undergo baseline brain MRI or contrast enhanced brain CT at screening. Again, patients unable to receive either will proceed with CT brain imaging without IV contrast. For those patients who have stable brain metastases present at baseline, brain imaging will be performed at each tumor assessment. For those patients without baseline brain metastases, brain imaging with MRI or CT will only be performed when clinically indicated and if new brain metastases are suspected.

All CT scans will be performed assuming ≤5 mm thickness. FDG-PET/CT or ultrasound measurements will not be allowed in lieu of MRI/CT for tumor assessments in this protocol. If a new lesion is identified by ultrasound during study duration, CT and/or MRI should be used for confirmation and inclusion of information.

If feasible, the same imaging technique should be used to characterize each identified and reported lesion at baseline screening and in follow-up tumor assessments. Tumor assessments will be performed at the end of every 8 weeks for the first 12 months of study drug therapy. After 12 months, radiographic assessments are obtained every 12 weeks. Timing of disease assessments should follow calendar days and should not be adjusted for delays in cycle start times. The allowable time windows for tumor assessments is ±7 days. Best response to treatment will be determined by iRECIST (further details are provided in section 12.0). Date of progression will be determined for progression-free survival analysis in secondary endpoint review by RECIST v1.1. Although a clear progression of non-target lesions without progression of target lesions is rare, the opinion of the treating physician should prevail in all circumstances. Tumor assessments will continue until disease progression or if a patient discontinues therapy due to reasons other than progression, including toxicity.

10.6 Treatment Beyond Progression

Immune checkpoint blockade agents including avelumab may produce anti-tumor effects by potentiating immune effector responses, and responses may be delayed compared to typical response patterns seen with targeted or cytotoxic agents. Clinical responses may include an initial increase in tumor burden and/or appearance of new lesions with then eventual regression of disease, termed “pseudoprogression”. Therefore, if radiographic imaging shows disease progression, tumor assessment should be repeated 4 weeks later to confirm true progressive disease (PD) per iRECIST criteria (*68*). Patients may also continue to receive investigational agents at the investigator’s discretion if the patient is determined to be clinically benefiting, as defined by:

1. No declines in ECOG performance status
2. Absence of rapid progressive disease by radiographic imaging
3. Absence of clinical signs or symptoms of disease progression (including worsening laboratory values)
4. Absence of progressive tumor at critical anatomic sites (i.e. cord compression), which may require urgent or emergent alternative medical interventions

The investigator’s judgement should be based on the overall benefit risk assessment and the patient’s clinical condition including performance status, clinical symptoms, adverse events, and laboratory data. Before therapy continues at confirmed progressive disease (PD) per iRECIST criteria (*63)*, investigators must discuss allowance with the PI, and the patient must be re-consented to this protocol with the understanding that they may be foregoing approved therapy options with possible clinical benefit.

10.7 Schedule of Activities

Activity	**Screening**			**Cycle 1-3+**				**Follow-Up**		
	≤28 days	**C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3+ D1**	**C3+ D15**	**End of Treatment (EOT)***	**Short Term Follow-Up**	**Long Term**
Visit Window*		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 30 days	± 7 days	± 28 days
Informed Consent[1]	**X**									
Medical History[2]	**X**									
Pathology Review[3]	**X**									
Optional Tissue Biopsy[4]	**X**			**X** (± 7 days)						
Height[5]	**X**									
Physical Examination[5]	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	
Vital Signs[5]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
ECOG Performance Status[6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Hematology[7]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chemistry[7]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

Amylase, Lipase, Total Protein[7]	**X**	Perform as clinically indicated								
Urinalysis[8]	**X**	Perform as clinically indicated								
Serum Pregnancy Test[9]	**X**	**X**		**X**		**X**		**X**		
Hepatitis B and Hepatitis C Serology Testing[10]	**X**									
Serum LDH	**X**									
Thyroid Function Testing[11]	**X**			**X**		**X**				
Optional Bone Scan[16]	**X**	Perform as clinicallyindicated								
Brain Scan[16]	**X**	Perform as clinicallyindicated								
12-lead ECG[12]	**X**	Perform as clinically indicated								
Talazoparib[14]		Continuous								
Premedication for Avelumab[15]		**X**	**X**	**X**	**X**	Optional administration per prior presence/severity of infusion reactions				
Avelumab		**X**	**X**	**X**	**X**	**X**	**X**			
Tumor Assessments (CT CAP w/ contrast OR CT chest + MRI A/P)[16]	**X**	Perform every 8 weeks for 56 weeks, then every 12 weeks thereafter until disease progression (±7 days)								

Research Blood Testing[17]		X		X		X		X		
Toxicity Assessments[18]	X	X	X	X	X	X		X	X	
Concomitant Treatment Use Assessment[19]	X	Monitored and Recorded Continuously						X		
Survival[20]										X

* End of Treatment (EOT) visit window may occur within 30 days of last dose.

1. Informed Consent must be obtained prior to undergoing any protocol-related procedures and must be obtained ≤28 days prior to enrollment onto study protocol.
2. Medical History Review: Review of the patient's medical history should be performed to allow for accurate screening and enrollment into protocol. This should include patient's prior cancer and non-cancer medical history, and concomitant medication use.
3. Pathology Review: Confirmation of existing documentation of renal cell carcinoma histology through a specialized genitourinary pathology review at Memorial Sloan Kettering Cancer Center.
4. Optional Tumor Biopsy: Patients may undergo screening tumor biopsy of primary or metastatic site, and on-treatment biopsy at Cycle 2 D1 (± 7 days).
5. Vital Signs will include blood pressure, pulse rate, temperature and weight. Height will be recorded on screening visit only. Full physical examination will be performed at screening, and subsequent visits should include focused physical exams of major body systems.
6. ECOG Performance Status must be documented in associated toxicity assessment sheet during visits per Appendix 1.
7. Laboratory Testing: Required safety laboratory tests will include: complete blood count (hemoglobin, platelets, white blood cell with differential), blood chemistry (AST, ALT, Alkaline Phosphatase, Sodium, Potassium, Chloride, Total Calcium, Total Bilirubin, Urea/BUN, Creatinine, Glucose (non-fasted), Albumin. Amylase, lipase and total protein are checked at baseline. These labs should be reviewed prior to study drug administration on Days 1 and days 15 of each treatment cycle.
8. Urinalysis: Urine dipstick for urine protein – if positive, collect microscopic reflex testing. Urine dipstick for blood – if positive, collect microscopic reflex testing.
9. Serum Pregnancy Testing: for women of childbearing potential, pregnancy test results must be reviewed prior to study drug administration on Day 1 of each treatment cycle. See section on childbearing potential (Section 6.1, Section 6.3), and monitoring (Section 10.4)

10. Hepatitis B and C Screening: HBV surface antigen, HBV core antibody, with HBV PCR performed reflexively if abnormal results. Screening for hepatitis C: anti-HCV antibody and HCV RNA PCR performed reflexively if abnormal results
11. Thyroid Function Testing: TSH, Free T4, Free T3
12. 12-lead ECG: ECG is to be obtained at screening and as clinically indicated at follow up visits. If mean QTc is prolonged > 500 msec, ECGs must be obtained to monitor serially during each day 1 of cycle visits.
13. Enrollment: patients meeting all entry criteria will be enrolled initiate investigational product administration preferable on the same day as enrollment. Product administration must begin within 5 days of enrollment.
14. Talazoparib Administration: On Day 1 and Day 15 of each treatment cycle, the daily dose of talazoparib should not be taken prior to the study visit and will be taken in the clinic after all assessments have been completed, and before the avelumab infusion. Drug supply will be considered when scheduling visit.
15. Premedication with Avelumab will be administered in the outpatient infusion suites on Days 1 and 15 of treatment cycle per Section 5.3. Premedication may be discontinued per presence/severity of infusion reactions seen during Cycle 1 and 2 at Cycle 3 per investigator.
16. Tumor Assessments: Assessments will be performed using iRECIST and RECIST v1.1. Baseline scans are to be performed within 28 days prior to the first dose of the study treatment. Baseline bone scans are to be performed if clinically indicated. Imaging should be performed with contrast agents unless strictly contraindicated for medical reasons. Timing of disease assessment should follow calendar days and should not be adjusted for delays in cycle starts. Tumor assessment should also be performed whenever disease progression is suspected per individual investigator. For patients who discontinue treatment for reasons other than PD, assessments should continue after end of treatment until PD. Repeat imaging obtained 4 weeks after initial documentation of response should be performed for response confirmation. End of Treatment (EOT) scan is not required.
17. Research Blood Testing: Peripheral blood will be collected for exploratory analyses prior to treatment initiation on C1D1, and serially during study. Details regarding collection methods are listed in the lab manual (Appendix 6).
18. Toxicity Assessments will be performed by CTCAE v5.0 grading (See Section 11.1)
19. Medication reconciliation will be performed at follow-up visits to ensure safe and appropriate concomitant medication use with study treatments.
20. Survival follow up will be logged at long-term follow-up appointments as described (Section 12.2) until start of new anti-cancer therapy, death, withdrawal of study consent or study discontinuation, whichever comes first.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Severity Assessments

All patients will be assessed for toxicity assessments per Common Terminology Criteria for Adverse Events (CTCAE) v.5.0., to describe the maximum intensity of adverse events. If the event is serious, the CTCAE grade must be documented and be consistent with the description of the CTCAE grade included in the narrative section of the serious adverse event report.

CTCAE grading is displayed by 1-5, with unique clinical descriptors for each severity of AE. The general guideline for this grading scheme relates to the severity of the AE, and follows:

Grade I	Mild, asymptomatic or mild symptoms. Clinical and diagnostic observations only, intervention may not be indicated.
Grade II	Moderate: minimal, local, or non-invasive intervention may be indicated. Limiting age-appropriate instrumental ADLs
Grade III	Severe or medically significant, but not immediately life-threatening: hospitalization or prolongation of hospitalization may be required. Limiting self-care ADLs, disabling.
Grade IV	Life-threatening consequences, urgent intervention is required
Grade V	Death related to adverse event

Table 8: CTCAE v5.0 General Grading Guidelines.

11.2 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in this protocol. All untoward events that occur after informed consent through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits and includes the new onset of or increase in pain during this period.

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade, and

relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the current version of the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE).

11.3 Relationship to Study Treatment

Assessment of the relationship of the AE to the study treatment by the investigator is based on the following two definitions:

Not-Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;

Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as de-challenge/re-challenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment. Possibly and probably related AEs should be documented as related.

11.4 Follow up of Adverse Events

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur more than 30 days after the decision to discontinue study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

11.5 Pregnancy and Fertility Assessments

Pregnancy testing is required at screening and recommended monthly until the end of the trial. Serum testing should be performed at screening and at the end of the study. Serum pregnancy testing should be performed at each new cycle visit every 4 weeks. There are no adequate data from the use of this combination in pregnant women. If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed up until the outcome of pregnancy is known. Women on trial should not breast feed.

11.6 Medication Errors/Overdose

Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting to Pfizer within 2 business days.

11.7 Talazoparib Toxicity

11.7.1 Hematologic Toxicity Related to Talazoparib

Myelosuppression related to talazoparib has been reported and usually requires dose adjustment as described below. The rate of grade ≥3 anemia, neutropenia, thrombocytopenia in solid tumor patients treated with talazoparib was 39%, 21%, and 15%, respectively, and this led to ultimate discontinuation of treatment in 0.7%, 0.3%, and 0.3% respectively. Myelodysplastic syndrome (MDS) / acute myeloid leukemia (AML) has been reported in 2/584 patients (0.3%) solid tumor patients treated with talazoparib in clinical trials. The duration of talazoparib treatment in these patients prior to developing MDS/AML was 4 months and 24 months, respectively, and both patients had a history of prior chemotherapy.

For grade ≥3 anemia, neutropenia, thrombocytopenia deemed related to study treatment, treatment with talazoparib must be interrupted with weekly blood counts until recovery is grade ≤1. At that time point, talazoparib can then be resumed with dose level reduction as outlined in Section 9.5.

Granulocyte colony stimulating factor (GCSF) may be administered to manage febrile neutropenic episodes per standard of care guidelines but should not be used routinely. Patients who require transfusion of packed red blood cells (PRBC) or platelet transfusion or growth factor support with GCSF must therefore undergo dose reduction upon recovery if study treatment is to be resumed. Growth factor support for anemia or thrombocytopenia is not permitted on the trial.

If hematologic toxicity has not recovered after 4 weeks in the absence of talazoparib, it will be strongly recommended that the patient undergo evaluation by benign hematology for further evaluation for etiology. If the patient does not have recovery to baseline within 4 weeks of dose interruption and/or the patient has undergone 2 dose reductions, then the patient should be discontinued from talazoparib.

If AML/MDS is diagnosed during this study, the patient must be withdrawn from the study.

Hematologic Toxicity	Talazoparib	Avelumab
Platelet Count 75-99, 1st occurrence	Study medication must be interrupted until platelet count is ≥100/uL with weekly CBC counts until recovery. If recovery within 4weeks, the study medication may be resumed at the same dose or reduced dose based on clinical judgement.	Continue as per schedule

Platelet Count 75-99/uL, 2nd occurrence	Study medication must be interrupted until platelet count is ≥100/uL with weekly CBC counts until recovery. If recovery within 4 weeks, the study medication may be resumed at the same dose or reduced dose based on clinical judgement. If 2nd treatment interruption occurs in <3 weeks after resuming from first occurrence, then dose reduction should be performed.	Continue as per schedule
Platelet Count < 75 /uL	Study medication must be interrupted until platelet count is ≥100/uL with weekly CBC counts until recovery. If recovery within 4 weeks, the study medication may be resumed at the reduced dose level.	1. Consider workup for immune related thrombocytopenia to evaluate causative role for avelumab. 2. Consider hold of avelumab and reinitiate avelumab once toxicity Grade ≤1 or baseline.
Absolute Neutrophil <1,000 / uL	Study medication must be interrupted until absolute neutrophil ≥1000 / uL with weekly CBC counts until recovery. If recovery within 4 weeks, the study medication may be resumed at the reduced dose level.	1. Consider hold avelumab and reinitiate avelumab once toxicity Grade ≤1 or baseline. 2. Permanently discontinue avelumab if the same Grade 3 toxicity recurs if talazoparib had already been discontinued and recurrent event occurs on avelumab only.
Hemoglobin <8 g/dL	Study medication must be interrupted until hemoglobin is ≥9 g/dL with weekly CBC counts until recovery. If recovery within 4 weeks, the study medication may	1. Consider workup for hemolytic anemia to evaluate causative role for avelumab. 2. Consider hold avelumab and reinitiate avelumab once toxicity Grade ≤1 or baseline.

	be resumed at the reduced dose level.	3. Permanently discontinue avelumab if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).

Table 9: Dose Modification Guide for Hematologic Toxicity for Talazoparib and Avelumab

11.7.2 Talazoparib Related Non-Hematologic Toxicity

In EMBRACA, the most common non-hematologic toxicities observed with single agent talazoparib (≥20%, all grade) was decreased appetite (21%), headache (33%), nausea (49%), vomiting (25%), diarrhea (22%), alopecia (25%), and fatigue (62%). The rate of these events at toxicity grade 3 was as follows: decreased appetite <1%, headache 2%, nausea <1%, vomiting 2%, diarrhea 1%, alopecia 0%, and fatigue 3%, and none of these adverse events were grade 4.

General management regarding talazoparib management in the setting of non-hematologic toxicity is outlined in Table 10. General guidelines regarding management of immune-related adverse events suspected to be from avelumab only is outline in later sections (starting Section 11.4).

For toxicities that are unequivocally related to talazoparib, not to avelumab, infusions of avelumab may continue per schedule even if talazoparib is held.

Talazoparib-related toxicity	**Talazoparib**
Grade 1	No changes indicated
Grade 2 Laboratory toxicities, non-heme	• Repeat laboratory assessment within 7 days; • continuation of talazoparib per investigator's discretion.
Grade 2 Non-Laboratory toxicities, non-heme	• Repeat investigator assessment in 7-14 days • continuation of talazoparib per investigator's discretion.
Grade 3	• hold talazoparib, unless toxicity deemed not clinically significant (e.g. increase amylase / lipase without imaging or clinical correlate of pancreatitis) • Resume talazoparib if toxicity resolves to Grade≤1 or baseline within 4 weeks of dose interruption. • If the same Grade 3 toxicity recurs, reduce by 1 dose level. • Permanently discontinue if toxicity does not improve to Grade 1 or baseline within 4 weeks.

	• Exceptions are laboratory values that do not have any clinical correlate.
Grade 4	Permanently discontinue talazoparib unless laboratory values do not have a clinical correlate

Table 10: Dose Modification Guide for Non-Hematologic Toxicity for Talazoparib and Avelumab

11.7.3 Talazoparib Related Gastrointestinal Toxicity

Gastrointestinal adverse reactions have been reported with talazoparib. In ≥20% of solid tumor patients treated on EMBRACA, all grade events included nausea (49%), vomiting (25%), and diarrhea (22%). Rates of grade 3 events for nausea, vomiting and diarrhea were <1%, 2%, and 1%, respectively, with no grade 4 events reported.

Rates of gastrointestinal lab parameter changes have been reported with talazoparib. In >20% of patients at all grade, the rate of increase in glucose (54%), increase in aspartate aminotransferase (AST) (37%), increase in alkaline phosphatase (36%), and increase in alanine aminotransferase (ALT) (33%). Grade 3-4 events for each lab parameter occurred with an increase in AST 2%, increase in alkaline phosphatase 2%, ALT 1%.

Guidelines regarding talazoparib management in the setting of gastrointestinal toxicity can be followed per non-hematologic toxicity guide in Table 10.

11.8 Avelumab Toxicity

11.8.1 Avelumab Related Pulmonary Toxicity

Pulmonary adverse events have been observed following treatment with avelumab, including a fatal case with monotherapy avelumab. In the combined safety data of solid tumors (*67*), pneumonitis occurred in 1.2% of patients, and among the 21 patients the median time of onset was 2.5 months and duration were 7 weeks (range 4 days-4+ months). All patients were treated with systemic corticosteroids, and resolution occurred in 12/21 (57%) patients at time of data cut-off. The majority of patient reported cases are grade 1 or 2, with study participants presenting with either asymptomatic radiographic changes (i.e. focal ground glass opacities, patchy infiltrates etc.) or with symptoms of dyspnea, cough or fever. Subjects with reported grade 3 or 4 pulmonary AEs were noted to have severe symptoms with more extensive radiographic findings and hypoxia.

Asymptomatic patients may be initially managed with consideration of dose delay, per investigator's judgement. Subjects with grade 2 pneumonitis will be managed with dose delay and treatment with corticosteroids. In subjects who do not initially respond to corticosteroids, anti-tumor necrosis alpha (anti-TNFa) therapies like infliximab and/or other immunosuppressants like cyclophosphamide may be considered. Please see Appendix 4 for toxicity related algorithm.

11.8.2 Avelumab Related Gastrointestinal Toxicity

Gastrointestinal AEs have been observed following treatment with avelumab. Most of cases of diarrhea were low grade (grade 1-2), with colitis occurring less frequently than diarrhea. High grade cases of diarrhea and colitis were managed are to be managed with corticosteroid use and/or non-steroidal immunosuppressants as detailed in toxicity related algorithm (please see appendix 4).

Immune mediated colitis occurred in 1.5% (26/1738 patients), and all patients were treated with corticosteroids with 15/26 patients (58%) receiving high dose corticosteroids. Resolution occurred in 18/26 patients (70%) at the time of data cut off, with median duration of colitis 6 weeks.

Hepatic adverse events including elevated liver function tests, and infrequently, drug induced liver injury, have been observed in patients following treatment with avelumab. Most cases are low or moderate grade, with higher-degree of hepatic adverse events management with corticosteroids (with or without mycophenolate mofetil). Early recognition and treatment of elevated LFTs and DILI are critical for medical management. If patients notice jaundice, or if they develop bruising, bleeding or right sided abdominal pain, they should be advised to seek medical management immediately. As LFT abnormalities are also common in patients with malignancy, it is important to distinguish whether LFT changes are due to infection, progression of disease, concomitant medications, alcohol etc. Please see Appendix 4 for toxicity related algorithm.

Immune mediated hepatitis occurred in 0.9% of patients receiving avelumab and led to the discontinuation in 0.5% of patients (9/1738 patients). Among the 16 patients who demonstrated immune mediated hepatitis, median time to onset was 3.2 months, and median duration of hepatitis was 2.5 months, and all patients were treated with corticosteroids for a median of 14 days. Resolution of hepatitis occurred in 9/16 patients (56%) at time of data cut off.

11.8.3 Avelumab Related Endocrine Toxicity

Endocrinopathies may occur during or after treatment with avelumab, and therefore continued monitoring during and after treatment is needed. Immune mediated thyroid disorders occurred in 6% of patients (98/1738 patients), with the majority of hypothyroidism (5%) of patients. Most cases of thyroid related disorders (hypothyroidism/hyperthyroidism) are found with changes in thyroid function testing. The median time to onset was 2.8 months, and immune mediated thyroid disorders resolved in 7% (7/98) patients. More than 1 organ involvement can be seen (i.e. thyroid disorder and adrenal disorder). Moderate and high-grade cases are treated with hormone replacement therapy, with or without the addition of corticosteroids. Guidelines for the recommended management of endocrine related toxicity is provided in Appendix 4.

Avelumab has been found to cause type I diabetes mellitus (diabetic ketoacidosis) and occurred in 0.1% (2/1738) of patients including two cases of grade 3 hyperglycemia which

led to permanent discontinuation. Avelumab has also been found to cause adrenal insufficiency, occurring in 0.5% (8/1738) of patients. All patients were treated with subsequent corticosteroids.

11.8.4 Avelumab Related Skin Toxicity

Dermatologic conditions including rash, pruritis has been seen following treatment with avelumab. Rashes that occur are most typically maculopapular in appearance, occurring in the trunk, back or extremities. In some cases, the rash and pruritis resolves without intervention, and in others, topical corticosteroids and anti-histamines are used for the rash and pruritis, respectively. Severe cases respond to systemic corticosteroids. Guidelines regarding the recommended management of skin AEs are provided in Appendix 4.

11.8.5 Avelumab Related Renal Toxicity

Elevated creatinine, as well as biopsy proven tubulointerstitial nephritis and allergic nephritis are infrequently observed during treatment with avelumab. Subjects with RCC or prior nephrectomy do not appear to be at higher risk. Immune mediated nephritis occurred in 0.1% (1/1738) patients and was permanently discontinued in this patient. Please see Appendix 4 for toxicity related algorithm.

11.8.6 Avelumab Related Neurologic Toxicity

Neurologic adverse events have been uncommonly described following treatment with avelumab. Neurologic adverse events may manifest as central abnormalities (i.e. aseptic meningitis, encephalopathy, or encephalitis), or peripheral sensory/motor neuropathies (i.e. myasthenia gravis, Guillan-Barre syndrome). Recommended management of neurologic AEs is provided in Appendix 4.

11.9 Combination Talazoparib / Avelumab – Dose Modifications for Treatment-Emergent, Unrelated Adverse Events

Per FDA label, unrelated Grade 2 renal impairment will require talazoparib dose reduction to at most dose level -1 since the drug is renally cleared.

For grade 3 toxicities related to study treatment both agents should be placed on hold during diagnostic workup & AE management; once either drug deemed to have no causative role in the development of the adverse event, that agent may be resumed per treating investigator's discretion, while the other drug (the one deemed causative) is held / dose-modified / discontinued as per drug-specific guidelines in the protocol (see Section 11, above).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Measurable disease is defined by disease that is accurately measured in at least one dimension (further details below). All tumor assessments will then be recorded in mm. All

patients will be evaluated by iRECIST and RECIST v1.1, Appendix 2 (*68*). Patients are evaluable for the primary endpoint if they have received at least 50% of the planned doses for each agent during Cycle 1. Patients who have taken less than 50% of the planned doses during Cycle 1 will be replaced for the primary endpoint, but will be evaluated in all safety and correlative analyses. Patients who have taken at least 50% of the planned dose but do not have a second tumor scan due to toxicity will be counted as a failure for the primary analyses on efficacy. Note, given unpublished data on this drug, we anticipate inevaluability and patients not receiving a second scan to be a rare if not unobserved event.

The following criteria will apply to target and non-target lesions:

1. Previously irradiated lesions: Lesions that are previously irradiated will not be considered measurable unless progression is documented radiographically previously or if a biopsy confirms persistence of disease ≥ 90 days following completion of therapy.
2. Malignant Lymph Nodes: Lymph nodes are considered pathologically enlarged and measurable if >15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short-axis will be used in measurement.
3. Measurable disease, other: Visceral lesions are considered measurable if the longest diameter measures >10mm.
4. Non-measurable disease: Lesions that include small lesions (longest diameter <10 mm) or pathological lymph nodes with <15 mm in short axis will be considered non-measurable. Bone lesions without extraosseous component, leptomeningeal disease, malignant ascites, pleural/pericardial effusion, lymphangitic disease, inflammatory breast disease is not considered measurable.
5. Target Lesions: Up to five selected measurable lesions (maximum of 2 lesions per organ), will be identified as target lesions by the study radiologist to represent relevant distribution of disease burden and will be measured and recorded at baseline. Target lesions should be reproducibly measured in follow up. It may be the case that the largest lesions do not lend themselves to reproducibility, at which point next largest lesions should then be selected. A sum of the diameters of the longest for non-nodal lesions and short-axis for nodal lesions should then be used for the target lesion calculation and the sum of diameters should be used for baseline. The baseline sum will be used as a reference to further characterize any objective tumor response.
6. Non-Target Lesions: All other lesions or sites of disease including measurable lesions over the 5 target lesions chosen should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or unequivocal progression of these should be noted during follow-up imaging.
7. Cystic Lesions: Cystic lesions that meet requirements for radiographic simple cysts should not be considered malignant. Cystic lesions that are thought to represent metastases can be considered measurable if they meet the above criteria.
8. Clinical lesions: clinical lesions will only be considered measurable when they are superficial (i.e. skin nodules, palpable lymph nodes), and >10 mm in diameter when

assessed using calipers. In the case of skin lesions, documentation by color photography including ruler to estimate size of lesion is required if used for follow-up.

Target Lesions	
Complete Response (iCR)	Disappearance of all target lesions. Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (iPR)	At least 30% decline in the sum of diameters of target lesions as compared to the reference baseline sum of diameters.
Unconfirmed Progressive Disease (iUPD)*	At least 20% increase in the sum of diameters of target lesions compared to the reference of the smallest sum of the study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of 20%, sum must demonstrate an absolute increase of at least 5 mm. This will need to be confirmed with imaging for iCPD assessment to be performed 4 weeks (± 7 days) later.
Stable Disease (iSD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, compared to reference of the smallest sum of diameters while on study
Non-Target Lesions	
Complete Response	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size <10 mm
Non-CR / Non-PD	Persistence of one or more non-target lesions
Unconfirmed Progressive Disease (iUPD)*	Appearance of one of more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should be representative of overall disease status changes and not single lesions increases.
Treatment beyond iUPD / Confirmation of disease progression	
Confirmed Progressive Disease (iCPD)	If further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following: - if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD OR - Further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)

	OR - further increase in the sum of measures ≥5 mm; otherwise assignment remains iUPD OR - further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression) OR - further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified OR - increase in the size or number of new lesions previously identified

Table 11: iRECIST Criteria for Response Guidelines. Adapted from (*68*).

*If iUPD remains unconfirmed at the next assessment, then the appropriate response will be assigned (iSD, iPR or iCR). Prior iUPD does not preclude subsequent iCR, iPR, or iSD on further assessments or as best overall response provided that iCPD is not documented at the next assessment after iUPD.

In the case of dose interruptions, the next cycle should follow the patient's original calendar schedule. Treatment cycle timing will not be delayed for treatment interruptions and therefore tumor assessments should continue to occur according to the original schedule regardless of whether study treatment is interrupted. If the patient discontinues treatment prior to confirmed disease progression, tumor imaging should continue at the specific time intervals until progression or until the start of subsequent anti-cancer therapy. Disease progression assessments outside of the scheduled windows will not be disregarded.

Patients may be treated by investigator pending radiology read on Day 1 of treatment cycle after clinical assessment. If assessment subsequently determines iCPD the study team will contact the patient to discontinue talazoparib unless the study team determines that the patient is to continue treatment beyond confirmed progression per section 10.6.

12.1 Calculated Study Endpoints

1. Objective Response Rate (ORR): proportion of patients with confirmed complete response (iCR) or partial response (iPR) assessed by iRECIST, relative to the total population of patients evaluable after 4 months. Confirmed responses are those that persist on repeat imaging 4 weeks after initial documentation of response. The final best response rate will be calculated 4 months after last patient accrued.
2. Progression-free Survival (PFS): duration of time from start of treatment until death or progression of disease by RECIST v1.1. Patients who are progression-free at time of analysis will be censored at the time of last valid tumor assessment. Patients with 2 or

more consecutive tumor assessments missing will be censored at last valid tumor assessment.

3. Overall Survival (OS): duration of time from start of treatment until death of any cause of study participants. Patients who are still alive at the time of analysis and those lost to follow-up will be censored at the time of last follow up.

12.2 Short-Term and Long-Term Follow Up

All patients would continue to be followed for safety every 30 days (± 7 days) through 90 days in short-term follow up, and then every 12 weeks (±14 days) in long-term follow up until the start of new anti-cancer therapy, death, withdrawal of study consent, or study discontinuation, whichever comes first.

Patients with ongoing treatment related toxicity following study treatment discontinuation will be followed at least every 4 weeks until the toxicity resolution or by clinical judgement by study investigator for expectation of further improvement. If a patient has discontinued study treatment for reasons other than disease progression, patient should continue to undergo assessments during the short-term follow period (+ 90 days) as if they were still on therapy, until new anti-cancer therapy starts. For long-term follow up procedures, visits may be conducted in the outpatient clinic or by remote contact by telephone.

12.3 Study Research Plan

Tumor Tissue

Archival tumor tissue will be requested from patients who have undergone biopsy or tumor resection as part of routine clinical care prior to study participation. Patients may undergo pre-treatment biopsy during the screening period if archival tissue is insufficient for baseline analysis.

Optional tumor biopsies of the primary renal mass or metastatic sites will be offered to all patients, to be performed during screening (within 28d of Cycle 1 D1) and at Cycle 2 D1 (± 7 days). While not a requirement, every effort should be made to perform a tumor biopsy at confirmed disease progression or if a patient discontinues study treatment due to disease progression, except in instances where the procedure poses an unacceptable risk to the patient in clinical research setting. Tumor specimen may include nephrectomy or metastatic site specimen and should include 4 core biopsy specimens.

Sample Preparation and Transport

Fresh tissue: On the date of biopsy, part of the specimen will be transported to the Chan Lab. Two core biopsies will be utilized for RNA/DNA extraction, 1 core biopsy will be snap frozen, and 1 core biopsy will be formalin fixed and paraffin embedded. Portions of tumors and normal tissue can then be prepared for further storage and analysis per laboratory guidelines. This will include placement of portions of tissue in aliquoted conical tubes in RPMI solution in TPS. The snap frozen specimens may be then stored for future investigation, including micro- and microdissection as well as for DNA/RNA extraction, and ultimately stored at -80ºC.

Archival Tissue: If available, 1-2 paraffin embedded tissue blocks containing formalin-fixed tumor slides will be requested. Paraffin blocks may then be processed according to standard institutional protocol, with final preparation of 20 unstained slides for available analysis. Specifications regarding tumor acquisition, sample processing, and exploratory analyses planned are detailed in the protocol's laboratory manual (Appendix 6).

All specimens will be delivered with the attached specimen submission form. All tissue will then be stored at the Chan Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY). Samples will be processed for in-depth biomarker investigation, including nucleic acid extraction for next generation sequencing analysis and mass spectrometry-based approaches as detailed in protocol's laboratory manual (Appendix 6).

Peripheral Blood Samples

Peripheral blood samples will be collected serially, processed and stored for all patients registered on the trial. This will include Vacutainer CPT whole blood tubes, EDTA whole blood tubes for plasma processing, and Streck BCT tubes for circulating tumor DNA assessments. Additional details on the collection plan, sample processing and storage are provided in the protocol's laboratory manual (Appendix 6).

Time Points: C1D1, C2D1, C3D1, C5D1+ (every 8 weeks), End of Treatment

Materials and Collection:

	Study Time Points**			
Materials§	C1D1*	C2D1 & C3D1	C5D1+ (every 8 weeks)	End of Treatment*
Vacutainer CPT Tubes (8mL/each tube)	X (3 tubes)	X (2 tube)	X (2 tube)	X (3 tubes)
Streck BCT Tube (10mL/each tube)	X (1 tube)	X (1 tube)	X (1 tube)	X (1 tube)
EDTA Tube (6cc/each tube)	X (1 tube)	X (1 tube)	X (1 tube)	X (1 tubes)

Table 12: Peripheral Blood Sample Schedule

*All blood draws should occur prior to avelumab administration. Collections may occur ±7 days of specified time point.

**An additional two blood draws at different time points beyond those listed is permitted when feasible based upon clinical / immunological findings

§Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Peripheral Blood Sample Preparation

Vacutainer CPT Tubes: The BD Vacutainer CPT Tube (Catalog: 362761), or equivalent, will be used. For collection, standard phlebotomy will fill tubes with 8 mL of blood, with attempt to obtain full 8 mL during collection attempt. The tube will then be inverted several times after collection to ensure adequate mixing. The patient's name, MRN, adhesive stickers will be attached to the tube. The date/time will be noted on the collection requisition form. The RSA will then deliver all specimens to Chan Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY).

Streck Tubes: The Streck Cell-Free DNA BCT tube (Streck Catalog No 218961), or equivalent, will be used. For collection, standard phlebotomy will fill each tube with 10 mL of blood, with attempt to obtain full 10 mL during collection attempt. The tube should be inverted several times after collection. The patient's name, MRN should be documented on adhesive stickers to each tube. The date/time will be noted on the requisition form, and the tubes will be placed in a biohazard bag at room temperature. The RSA will then deliver all specimens to Chan Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY).

EDTA Tubes: The BD lavender tube (BD Catalog: 367863) will be used. For collection, standard phlebotomy will fill each tube with 6 mL of blood, with attempt to obtain full 6 mL during collection attempt. The tube should be inverted several times after collection. The patient's name, MRN should be documented on adhesive stickers to each tube. The date/time will be noted on the requisition form, and the tubes will be placed in a biohazard bag at room temperature. The RSA will then deliver all specimens to Chan Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY). Samples may then be stored at -80ºC per standard practice procedure for future analysis.

Data Entry for Specimen Collection

MSKCC RSA and/or Chan laboratory personnel will collect information into a secured database once samples are collected and transported. If a sample is not fully collected, the reasoning for incomplete or partial collection should be documented into the database as well for accurate records.

Select Corelative Planned Studies

Select studies include:

1. Tissue whole exome sequencing, specifically identifying
    a. DDR Mutations / Homologous Recombination Deficiency (HRD) Mutations: 3 DNA based HRD-scoring algorithms will be generated, including HRD loss of heterozygosity score (LOH), HRD telomeric allelic imbalance score (TAI), and HRD large scale transition score (LST). Select genes to be included in evaluation include *BRCA1, BRCA2, PARP1, ATM, ATR, RAD51C, BAP1, PALB2, MRE11, BARD1/BRIP1, RAD50/51/51B/51D, ERCC2, ERCC3, ERCC4, ERCC5, MMR* genes*, POLE, FANCC, FANCA, BLM, CHEK1, CHEK2, RB1, ATRX* as well as others.

   b. Tumor Mutational Burden: Tumor mutational burden is defined as the total number of mutations in the genome, or number of mutations per DNA mega base if derived from targeted sequencing. This analysis will include evaluation of INDELs, breakpoint locations and structural rearrangements.
2. Tumor RNA Sequencing: This will focus on immune deconvolution via computational methods including CIBERSORT and single sample gene expression analysis (ssGSEA) for Immune Subset Profiling: Characterization of immune cell subsets based on PCR based T-cell receptor sequencing, IHC analysis (PD-L1 expression), and T-cell enrichment scores, as well as immune deconvolution as above in combination with flow cytometry data.
3. Metabolomics: Characterization of tissue specimens for oncometabolite expressions through mass spectrometry, with specific attention to fumarate and succinate levels as predicted changes in cohort 2 FH/SDH patients only.
4. FH/ SDH patients: FH and SDH Functional Assessment: With available tissue specimens, all patients in cohort 2 will undergo MSK-IMPACT testing for germline and somatic mutational testing. Further, all FH/SDH patient specimens may also undergo investigational immunohistochemical staining with research antibody testing (i.e. 2SC) to compare functional loss with genomic and state-approved *FH/SDH* assay testing.
5. RMC patients: while loss of SMARCB1 (INI1) is not part of eligibility it will be assessed in all patients who can provide archival tumor tissue.

Further specification regarding tumor acquisition, sample processing, and techniques used for exploratory analyses planned are detailed in the protocol's laboratory manual (Appendix 6).

In the course of this research it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service. If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:
• Participant Name/MRN #
• Type of Biospecimen (tissue, blood, saliva)
• Incidental Finding

• Collection Protocol #
• Contact: rtmgapirb@mskcc.org

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 Study Treatment Discontinuation

Reasons for study treatment withdrawal include, but are not limited to:

1. Voluntary withdrawal by the patient who is at any time free to discontinue clinical trial participation without prejudice for further treatment
2. Unacceptable toxicity: if attribute to only one of the two investigational study treatments, the investigator may continue treatment with the other investigational study treatment. If both medications have been interrupted for ≥8 weeks, the patient should be discontinued from the study treatment.
3. Progressive Disease: Patients with confirmed disease progression by iRECIST (iCPD) or patients who are no longer experiencing clinical benefit as determined by investigator should be discontinued from study treatment. Patients with confirmed disease progression who are continuing to derive clinical benefit as assessed by treating physician may be eligible to continue study treatment, provided that the treating physician has determined that the risks and benefits remain favorable. Study drug discontinuation will be applied to all other cases of disease progression.
4. Global deterioration of health status
5. Risk to patient as determined by study team and treating physician
6. Severe non-compliance as determined by investigator team
7. Incorrect enrollment of patient (i.e. patient does not satisfy inclusion or exclusion criteria on review)
8. Patient becomes pregnant or starts breast feeding during clinical trial
9. Patient is lost to follow up
10. Significant protocol deviation
11. Study termination by trial sponsor
12. Necessity for other anti-cancer therapy
13. Sexually active patients who refuse to use medically accepted methods for contraception during this study and post-study completion (5 months for women, 7 months for men).
14. Study termination or hold by regulatory agencies
15. Death

Any patient who discontinues study drugs should be seen at 30 days post-discontinuation treatment for clinical assessment. At that time, patient's tumor status should be assessed clinically, and if appropriate, disease status or progression should be confirmed by radiographic assessment. The investigator will provide best available observation, tests, and evaluation, and complete safety assessments for the patient given clinical trial participation. After the discontinuation of all medications, all ongoing AEs must be followed for resolution, unless deemed unlikely to resolve due to underlying disease by treating

physician. Any new AEs that develop in the 30 days period post study treatment discontinuation should also be assessed in the setting of late onset immune related adverse events. Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration. Patients should also be continually followed as per iRECIST and RECIST v1.1.

Patients should be followed for survival follow-up, unless otherwise specified including:

1. Patient refuses follow-up
2. Patient is lost to follow-up
3. Study is terminated by sponsor
4. Death

13.2 Voluntary Withdrawal of Consent

Patients may withdraw consent from clinical trial participation at any time at their own request, or they may be withdrawn at the discretion of the investigator team for safety, behavioral reasons, or inability to comply with protocol related procedure. The patient is free from prejudice regarding future care or treatment.

If a study participant does withdraw from clinical trial participation, the patient should continue to be followed for survival unless the patient additionally withdraws consent for disclosure of future information or for further contact from study team. In that case, no study specific evaluation should be performed, and no additional data will be collected. Patients should then notify the investigator in writing of the decision to withdrawal consent from future follow up. Upon withdrawal, all unused talazoparib should be returned and the patient should be requested to return for final return visit for drug return and to follow up with the patient on any unresolved AEs. The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from only further receipt of investigational drug or also from study procedure and/or post-treatment follow up. For vital status follow up (i.e. whether the patient is alive or dead), publicly available information should also be used as directed in accordance to local law.

13.3 Lost to Follow-Up

If a study participant does not return for a protocol related scheduled visit, every effort should be made by the study team to contact the patient and report upon the ongoing status. All attempts to contact the patient and information received during contact must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome if possible. Patient will be deemed lost to follow-up by the inability to reach the patient after a minimum of 2 documented phone calls, emails or faxes, and lack of response by the patient to an additional 1 registered mail letter. If, after all attempts, the patient remains lost to follow-up, then the last known alive data as determined by the study team should be reported and documented in the patient's medical record.

14.0 BIOSTATISTICS

For both cohorts, the primary endpoint will be best ORR as measured after 4 months, with independent secondary endpoints including PFS and OS as calculated below:

1. Objective Response Rate (ORR): proportion of patients with confirmed complete response (CR) or partial response (PR) assessed by iRECIST after 4 months from the start of therapy, relative to the total population of patients evaluable. Confirmed responses are those that persist on repeat imaging 4 weeks after initial documentation of response, and if not, they will otherwise be counted as a non-responder during assessment of ORR. Additionally, patients with inadequate data for tumor assessment will be considered as non-responders. The two-sided exact 90% confidence intervals for ORR will be calculated. The final best response rate will be calculated 4 months after last patient accrued.
2. Progression-free Survival (PFS): duration of time from start of treatment until death or progression of disease. Patients who do not have an event (PD or death) will be censored on the date of last adequate tumor assessment. Additionally, patients who start new anti-cancer therapy prior to event or who have 2 or more missing tum or assessments will also be censored.
3. Overall Survival (OS): duration of time from start of treatment until death of any cause of study participants. Patients without an event (death) will be censored at the data of last contact.

14.1 Cohort 1 Enrollment and Statistical Plan

The primary endpoint is best overall response rate after 4 months of therapy. The first cohort is designed using optimal Simon two-stage design, allowing us to terminate the study at an interim timepoint if the data do not show preliminary efficacy. In stage 1, we will accrue 10 patients. If 1 or more have a response in the first 10 patients, we will continue for a total of 29 patients. If no responses are observed in the first 10 patients, then cohort 1 will be terminated early. If 4 or more of the 29 patients have a response, the study can be deemed a success. If the study stops early, or if 3 or less have a response, the study will not be deemed a success. If needed (i.e. patients in stage 1 are still on study and we have not observed 4 patients with a response), we will hold accrual prior to enrolling patients on stage 2.

This design discriminates between response rates of 5% versus 20% and assumes 80% power and a one-sided type I error of 5%. The probability of early termination under the null is 60%. A case report of RCC patients pre-treated with PD-1/PD-L1 inhibitors who then went on to receive a different PD-1 inhibitor has shown progressive disease as best response to therapy to subsequent PD-1 agent (*69*). There remains insufficient prospective data regarding the efficacy of immune checkpoint inhibitors (monotherapy or combination strategy) after progression through a prior immune checkpoint inhibitor therapy. Thus, since patients in Cohort 1 are refractory to PD-1/PD-L1 inhibitors, a 5% null rate was selected for this study.

As of October 2021, the cohort is now closed. The PI, Co-PI, and study team met to review and discuss study compliance, adverse events, toxicities, and overall response experienced by the first 10 patients enrolled in Cohort 1 on 10/11/2021. Patients were treated with talazoparib 1 mg PO daily and Avelumab 800mg IV Q2 weeks. All patients met the minimum dose exposure criterion as specified in the protocol (at least 50% of drug in the first cycle) and therefore all were considered evaluable for primary endpoint. All patients had follow-up evaluation by imaging, and if the imaging was performed prior to scheduled scan per protocol it was due to concern for early progressive disease. Upon summary review, no patients achieved an objective response per iRECIST criteria, and therefore the efficacy threshold was notmet to advance to stage 2 per protocol. Therefore, we have decided to close Cohort 1 as per study design.

14.2 Cohort 2 Enrollment and Statistical Plan

Cohort 2 includes rare sub-types of RCC including FH- and SDH-deficient RCCs and renal medullary carcinoma (RMC). Given the rarity of these cancers and considering limited historical data, the sample size for this cohort is not based on a formal delineation of a null and alternative hypothesis. All analyses of ORR, PFS and OS will be descriptive. It is feasible that we will accrue 15 patients in Cohort 2 in a reasonable timeframe. The maximum 90% exact confidence interval half-width for ORR in a sample size of 15 is 0.23. If we observe 1 response, the response rate and 90% exact confidence interval is as follows: 6.7% with 90% CI of (.34%, 27.93%).

For both cohorts, ORR will be estimated with a 90% confidence interval. PFS and OS will be estimated using Kaplan-Meier methods. Safety and tolerability will be summarized descriptively as frequencies. Compliance will be summarized by the calculating the amount of dose received over the study period.

14.3 Sample Size/Accrual Rate

The total planned size of cohorts 1 (29 patients total) and cohort 2 (15 patients). The anticipated accrual time for both cohorts at MSKCC is 3 years. This is based on the historic accrual patterns that are seen in early and large scale clear cell RCC clinical trials, that would account for the majority of cohort 1 enrollment. Cohort 2 consists of a rare subtype of RCC, and therefore estimation is more challenging regarding accrual patterns. In prior study of non-clear cell RCC, by which FH- and SDH- loss would be accounted for, 34 patients were accrued within 3 years at the MSK Manhattan site. Therefore, we expect accrual to this cohort to also be reasonably completed in this timeframe as well.

Patients are evaluable for the primary endpoint if they have received at least 50% of the planned doses for each agent during Cycle 1. Patients who have taken less than 50% of the planned doses during Cycle 1 will be replaced for the primary endpoint, but will be evaluated in all safety and correlative analyses. Patients who have taken at least 50% of

the planned dose but do not have a second tumor scan due to toxicity will be counted as a failure for the primary analyses on efficacy. Note, given unpublished data on this drug, we anticipate inevaluability and the number of patients not receiving a second scan to be a rare if not unobserved event.

14.4 Exploratory Analyses

Exploratory analyses of biomarkers for response to therapy will be performed in accordance to studies set forth in the protocol's laboratory manual (Appendix 6). Analyses will be separated by cohort given distinct genomic differences, and all analyses will be descriptive and graphical as noted below. Biomarker data will include baseline and on-treatment/end of treatment assessments of changes to biomarker data including, but not limited to, centrally assessed defects. Measures are detailed in section 12.3.

For all continuous measurements used in biomarker analysis, summary statistics (i.e. the mean, standard deviation, median, percent of coefficient of variation, and minimum/maximum levels) will be calculated at baseline and on treatment/end of treatment time points, as appropriate based on patient's available samples. Change from baseline measurements will be calculated.

For discrete measurement biomarkers (e.g., tumor marker status), frequencies and percentages of categorical biomarker measures will be determined at baseline and on treatment/post treatment time points, as appropriate; shift tables may also be provided.

Data from biomarker assays will be analyzed using graphical methods. Specifically, we will graphically examine the relationship between the biomarkers and measures of efficacy, such as ORR and progression free survival. If the data allow, these relationships will be tested using a Fisher's exact test, a Wilcoxon test, or a log-rank test as appropriate.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

N/A. No randomization in this study.

16. 0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to this research protocol. The responsibilities of the CRC include data collection, abstraction and entry, aid in adverse reporting, sponsor communication, audit preparation, and generation of registration reports. The data collected for this study will be entered into a secure database (Medidata). The principal investigator will maintain ultimate responsibility for the clinical trial.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor for patient accrual and completeness in registration data. Routine data quality reports will also be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study duration. Potential issues will be brought to the attention of the study team for discussion and action at protocol related meetings. Random sample data quality and protocol compliance audits will the conducted by the study team.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DMS Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://mskweb2.mskcc.org/irb/index.htm There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g. Protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Study Treatment Accountability

The primary investigator and study team will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept

regarding the date, lot number, and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

16.4 Conditions for Protocol Modification

Protocol modifications including amendments may be made and will be prepared, reviewed and approved by representatives of the investigator. Protocol modifications or amendments must be reviewed by Pfizer prior to implementation.

All protocol modification must be submitted to the IRB for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (i.e. change in telephone number).

16.5 Conditions for Termination of Study

At any time, the study may be terminated by MSKCC or Pfizer. Should this be necessary, Pfizer and MSKCC will arrange the procedures on an individual study basis after review and consultation. Adequate consideration is given for the protection of the subject's interest. Upon study termination, MSKCC shall cease enrolling subjects into the study, and shall discontinue study conduct as soon as medically practicable.

17.0 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible. Up to 44 patients will be enrolled on study. Patients eligible will be 18 years of age or older with an ECOG 0-2. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because this disease does not occur or occurs rarely in participants under 18 years. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of

informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side-Effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Benefits: There is a potential benefit to society, in that a successful study could lead to a larger phase II or III trial which would improve our understanding of the treatment of these diseases and potentially extend survival for patients with RCC. Participation in this study may not provide any benefit to the individual participant, and may or may not provide information which will ultimately benefit others.

Costs: The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include administration of avelumab, hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG and doctor's fees. However, Pfizer will provide a supply of talazoparib and avelumab at no cost to the patient. Patients will not be charged for correlative research work that is included in this trial. Patients will be responsible for the costs of standard medical care, including complications of treatment. Non-billable tests include the tests performed for research purposes.

Incentives: No incentives will be offered to patients/subjects for study participation.

Alternatives: The alternative to this trial would be treatment with standard cytotoxic chemotherapy, immunotherapy or participation in alternative clinical trial.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel, the FDA, and/or other governmental agencies) may review patient records as required.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring committee established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

All parties will ensure protection of patient personal data and will not include patient names, or other identifiable data in any reports, publications or other disclosures, except if required by law. The investigator will maintain a confidential list of patients who participated in this study, linking each patient's numerical code to his or her actual identity.

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the Research Authorization that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantialdisruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30 -day period that is unexpected and at least possibly related to protocol treatment must be reported .

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

Any overdose or study drug administration error that results in SAE even if it does not meet the criteria for definition of SAE.

17.2.1 SAE Reporting to Pfizer

All serious adverse events that occur after the patients' written consent to participate in the study through 28 days of discontinuation of dosing must be reported to Pfizer, whether related or not related to the study drug. If applicable, SAEs must be collected that relate to any later protocol specific procedures.

Following the subject's written consent in the study, all SAEs, whether related or not related to study drug, are collected including those thought to be associated with protocol specific procedures. The investigator should report any SAE occurring after these time

periods, which is believed to be related to study drug or protocol-specified procedure. An SAE report must be completed for any event where doubt exists regarding its seriousness. SAEs that occur after completion of the reporting time as defined above are reportable to Pfizer if the Investigator suspects a causal relationship between the Pfizer product and the SAE.

The time frame for reporting an SAE to Pfizer is immediately upon awareness if the SAE is fatal or life-threatening (i.e. causes an immediate risk of death), regardless of the available information extent, or within 24 hours of first awareness of the SAE if the SAE is not fatal or life-threatening.

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

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

When new, updated, or corrected information about a previously reported SAE is obtained, a follow-up report should be submitted to Pfizer on a new SAE Report Form (or other agreed reporting method) that includes the data that are new or revised from the previous report. Follow-up information should never be added to a previously submitted report form. Ensure that any new events included on a follow-up report are marked as serious and a causality assessment is provided for each of them.

An occupational exposure is an exposure to a Pfizer product for human use because of one's occupation. An occupational exposure is reportable regardless of whether there is an associated SAE. An exposure during breastfeeding occurs if an infant or child may have been exposed through breast milk to the Pfizer product during breastfeeding by a female taking the Pfizer product. Exposure during breastfeeding is reportable to Pfizer regardless of whether there is an associated SAE in the infant or child. Exposure During Pregnancy occurs when a fetus (from pre-embryo to birth) may have been exposed at any time during pregnancy to a Pfizer product (or blinded therapy).

Contact information for submission of reportable events to Pfizer:

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

E-mail: USA.AEReporting@pfizer.com, specifying:

- PROTOCOL:
- SUBJECT:

- SITE/PI
- SAE/ONSET

MSK will provide Pfizer a redact internal serious adverse event (SAE) form.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: Eastern Cooperative Oncology Group (ECOG) Performance Status Chart

Appendix 2: iRECIST and RECIST v1.1. Guidelines

Appendix 3: Avelumab Infusion Related Events and Management

Appendix 4: Avelumab Immune Related Adverse Events and Management

Appendix 5: Talazoparib Medication Interactions

Appendix 6: Correlative Lab Manual

Appendix 1: Eastern Cooperative Oncology Group (ECOG) Performance Status Chart

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity, but ambulatory and able carry out light or sedentary nature (i.e. light house work, office work)	1
Ambulatory and capable of all self-care, but unable to carry out work activities. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3
Completely disabled, cannot carry on self-care. Totally confined to bed or chair	4
Death	5

Appendix 2: iRECIST and RECIST v1.1 Guidelines.

iRECIST and RECIST: The following criteria will apply to target and non-target lesions, adapted from Seymour et al. (*68*):

1. Previously irradiated lesions: Lesions that are previously irradiated will not be considered measurable unless progression is documented radiographically previously or if a biopsy confirms persistence of disease ≥ 90 days following completion of therapy.
2. Malignant Lymph Nodes: Lymph nodes are considered pathologically enlarged and measurable if >15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short-axis will be used in measurement.
3. Measurable disease, other: Visceral lesions are considered measurable if the longest diameter measures >10mm.
4. Non-measurable disease: Lesions that include small lesions (longest diameter <10 mm) or pathological lymph nodes with <15 mm in short axis will be considered non-measurable. Bone lesions without extraosseous component, leptomeningeal disease, malignant ascites, pleural/pericardial effusion, lymphangitic disease, inflammatory breast disease is not considered measurable.
5. Target Lesions: Up to five selected measurable lesions (maximum of 2 lesions per organ), will be identified as target lesions by the study radiologist to represent relevant distribution of disease burden and will be measured and recorded at baseline. Target lesions should be reproducibly measured in follow up. It may be the case that the largest lesions do not lend themselves to reproducibility, at which point next largest lesions should then be selected. A sum of the diameters of the longest for non-nodal lesions and short-axis for nodal lesions should then be used for the target lesion calculation and the sum of diameters should be used for baseline. The baseline sum will be used as a reference to further characterize any objective tumor response.
6. Non-Target Lesions: All other lesions or sites of disease including measurable lesions over the 5 target lesions chosen should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or unequivocal progression of these should be noted during follow-up imaging.
7. Cystic Lesions: Cystic lesions that meet requirements for radiographic simple cysts should not be considered malignant. Cystic lesions that are thought to represent metastases can be considered measurable if they meet the above criteria.
8. Clinical lesions: clinical lesions will only be considered measurable when they are superficial (i.e. skin nodules, palpable lymph nodes), and >10 mm in diameter when assessed using calipers. In the case of skin lesions, documentation by color photography including ruler to estimate size of lesion is required if used for follow-up.

In contrast to RECIST v1.1 guidelines, iRECIST guidelines:

1. Require confirmation of both progression and response by imaging at least 4 weeks from the date first documented
2. Does not necessarily score the appearance of new lesions as progressive disease if the sum of the lesion diameters of target lesions (minimum of 10 mm/lesion, maximum of 5

target lesions, maximum of 2 per organ), and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and technique should then be used to characterize each identified and reported target lesion(s) at baseline and throughout the study. Response assessment is defined then by the following:

Target Lesions:

1. Complete Response (iCR): Disappearance of all target lesions. Any pathological lymph nodes must have a reduction in short axis to <10 mm.
2. Partial Response (iPR): At least 30% decline in the sum of diameters of target lesions as compared to the reference baseline sum of diameters.
3. Unconfirmed Progressive Disease (iUPD): At least 20% increase in the sum of diameters of target lesions compared to the reference of the smallest sum of the study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of 20%, sum must demonstrate an absolute increase of at least 5 mm. This will need to be confirmed with imaging for iCPD assessment to be performed 4 weeks (± 7 days) later.
4. Stable Disease (iSD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, compared to reference of the smallest sum of diameters while on study.
5. Confirmed Progressive Disease (iCPD): If further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:
    - if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
    - Further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
    - Further increase in the sum of measures ≥5 mm; otherwise assignment remains iUPD
    - Further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression) OR
    - Further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
    - Further increase in the size or number of new lesions previously identified

Non-Target Lesions:

1. Complete Response: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size <10 mm
2. Non-CR / Non- PD: Persistence of one or more non-target lesions
3. Unconfirmed Progressive Disease (iUPD)*: Appearance of one of more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should be representative of overall disease status changes and not single lesions increases.

For RECIST guidelines, see below:
https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

RECIST v1.1 Response Criteria	
Target Lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least 30% decline in the sum of diameters of target lesions as compared to the reference baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, compared to reference of the smallest sum of diameters while on study
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.
Non-Target Lesions	
Complete Response	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size <10 mm in short axis.
Non-CR / Non-PD	Persistence of one or more non-target lesions and/or maintenance of tumor marker levels above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered progression.

Appendix 3: Avelumab Infusion Related Events and Management

NCI CTCAE Severity Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening. • Next scheduled infusion can be re-attempted at original rate, per treating investigator's discretion.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume avelumab infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening • Next scheduled infusion should be initiated at 50% of original rate. Added premedication should be considered.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the patient. • Patients must be withdrawn immediately from avelumab treatment and should not receive any further avelumab treatment.

Appendix 4: Avelumab Immune Related Adverse Events and Management

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5)	Initial Management	Follow-up Management
Grade 1 • **Diarrhea:** <4 stools/day over Baseline • **Colitis:** asymptomatic	• Continue avelumab therapy • Symptomatic treatment (eg, loperamide).	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately • If worsens, treat as Grade 2, 3 or 4
Grade 2 • **Diarrhea:** 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL • **Colitis:** abdominal pain; blood in stool	• Withhold avelumab therapy • Symptomatic treatment.	• If improves to Grade ≤1, resume avelumab therapy • If persists >5-7 days or recurs, treat as Grade 3 or 4.
Grade 3 to 4 • **Diarrhea (Grade 3):** ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL • **Colitis (Grade 3):** severe abdominal pain, medical intervention indicated, peritoneal signs • **Grade 4:** life-threatening, perforation	• Withhold avelumab for Grade 3 • Permanently discontinue avelumab for Grade 4 or recurrent Grade 3 • 1.0 - 2.0 mg/kg/day prednisone IV or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	• If improves, continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3) • If worsens, persists >3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contraindication). *Note: infliximab should not be used in cases of perforation or sepsis*
Dermatological irAEs		
Grade of Rash PFS(NCI-CTCAE v5)	Initial Management	Follow-up Management

Grade 1 to 2 Covering ≤30% body surface area	• Continue avelumab therapy • Symptomatic therapy (for example, antihistamines, topical steroids)	• If persists >1 to 2 weeks or recurs, withhold avelumab therapy • Consider skin biopsy • Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper • If worsens, treat as Grade 3 to 4
Grade 3 to 4 • **Grade 3:** Covering >30% body surface area • **Grade 4:** Life threatening consequences	• Withhold avelumab for Grade 3 • Permanently discontinue for Grade 4 or recurrent Grade 3 • Consider skin biopsy • Consider dermatology consult • Consider 1.0 - 2.0 mg/kg/day prednisone or equivalent • Consider addition of prophylactic antibiotics for opportunistic infections.	• If improves to Grade ≤1, taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3)
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5)	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	• Consider withholding avelumab therapy • Monitor for symptoms every 2 - 3 days • consider pulmonary and infectious disease consults	• Re-assess at least every 3 weeks • If worsens, treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	• Withhold avelumab therapy • Consider pulmonary and infectious disease consults • Monitor symptoms daily; consider hospitalization • 1.0 - 2.0 mg/kg/day prednisone or equivalent • Consider Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy.	• Re-assess every 1 to 3 days • When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper • If not improving after 2 weeks or worsening, treat as Grade 3 to 4.

Grade 3 to 4 • **Grade 3**: Severe new symptoms; New/worsening hypoxia; • **Grade 4:** Life-threatening	• Permanently discontinue avelumab therapy • Hospitalize • Consider pulmonary and infectious Disease consults. • 1.0 - 2.0 mg/kg/day prednisone or equivalent • Consider addition of prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	• If improves to Grade ≤1, taper steroids over at least 1 month • If not improving after 48 hours or worsening, add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5)	Initial Management	Follow-up Management
Grade 1 • AST or ALT >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal • And/or total bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	• Continue avelumab therapy.	• Continue liver function monitoring • If worsens, treat as Grade 2 or 3 to 4.
Grade 2 • >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal • and/or total bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	• Withhold avelumab therapy • Increase frequency of monitoring to every 3 days.	• If returns to Grade ≤1, resume routine monitoring; resume avelumab therapy • If elevation persists >5 to 7 days or worsens, treat as Grade 3 to 4.
Grade 3 to 4 >5.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal and/or total bilirubin >3.0 x ULN if baseline was normal; >3.0 x baseline if baseline was abnormal	• Permanently discontinue avelumab therapy • Increase frequency of monitoring to every 1 to 2 days • 1.0 - 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist/ hepatologist • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	• If returns to Grade ≤1, taper steroids over at least 1 month • If does not improve in >3 to 5 days, worsens or rebounds, add mycophenolate mofetil 1 gram (g) twice daily • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5)	Initial Management	Follow-up Management

Grade 1 **Creatinine increased >ULN to 1.5 x ULN**	• Continue avelumab therapy.	• Continue renal function monitoring • If worsens, treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	• Withhold avelumab therapy • Increase frequency of monitoring to every 3 days • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy • 1.0-2.0 mg/kg/day prednisone or equivalent.	• If returns to Grade ≤1, taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. • If worsens, treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN	• Permanently discontinue avelumab therapy • Monitor creatinine daily • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy • Nephrology consultation.	• If returns to Grade ≤1, taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	Initial Management	Follow-up Management
• New onset of cardiac signs or symptoms • and / or new laboratory cardiac biomarker elevations (e.g., troponin, CK-MB, BNP) • or cardiac imaging abnormalities suggestive of myocarditis.	• Withhold avelumab therapy • Hospitalize • In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management • Cardiology consult to establish etiology and rule-out immune-mediated myocarditis • Guideline based supportive treatment as per cardiology consult* • Consider myocardial biopsy if recommended per cardiology consult	• If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy • If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis
Immune-mediated myocarditis	• Permanently discontinue avelumab • Guideline based supportive treatment as appropriate as per cardiology consult* • 1.0-2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections	• Once improving, taper steroids over at least 1 month • If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A).

*Local guidelines, or e.g., ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs		
Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Continue avelumab therapy • Consider Endocrinology consult • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (i.e., hypopituitarism / hypophysitis)	• Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Withhold avelumab therapy • Consider hospitalization • Consider endocrinology consult • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate • Rule-out secondary endocrinopathies (i.e., hypopituitarism / hypophysitis).	• Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression) • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate

• **Hypopituitarism** • **Hypophysitis (secondary endocrinopathies)**	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e., subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Consider referral to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Consider pituitary MRI and visual field examination as indicated If hypophysitis confirmed: • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI • Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month • Consider addition of prophylactic antibiotics for opportunistic infections.	• Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement) • In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented • Continue hormone replacement/suppression therapy as appropriate
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	• Withhold avelumab therapy pending clinical investigation.	• If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy • If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	• Withhold avelumab therapy • 1.0 - 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Specialty consult as appropriate.	• If improves to Grade ≤1, taper steroids over at least 1 month and resume avelumab therapy following steroids taper.

Recurrence of same Grade 3 irAEs	• Permanently discontinue avelumab therapy • 1.0 - 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Specialty consult as appropriate.	• If improves to Grade ≤1, taper steroids over at least 1 month.
Grade 4	• Permanently discontinue avelumab therapy • 1.0 - 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed • Add prophylactic antibiotics for opportunistic infections • Specialty consult.	• If improves to Grade ≤1, taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	• Permanently discontinue avelumab therapy • Specialty consult.	

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

Appendix 5: Prohibited Potent P-gp Inhibitors

Amiodarone
Carvedilol
Clarithromycin
Cobicistat
Dronedarone
Erythromycin
Glecaprevir/pibrentasvir
Indinavir
Itraconazole
Ketoconazole
Lapatinib
Lopinavir
Propafenone
Quinidine
Ranolazine
Ritonavir
Saquinavir
Sofosbuvir/velpatasvir/voxilaprevir
Telaprevir
Tipranavir
Valspodar
Verapamil

Appendix 6: Correlative Laboratory Manual

Tissue Specimen Collection and Storage

Time Points: Pre-treatment (optionally at screening), and during study period

Tumor Specimens:

- Fresh Tumor Biopsy: Tumor biopsies may be obtained for patients upon entry into clinical study during screening period, as well as while on-treatment. Tumor specimen may include nephrectomy or metastatic site specimen and should include 4 core biopsy specimens. On the date of biopsy, part of the specimen will be transported to the Chan Lab. Two core biopsies will be utilized for RNA/DNA extraction, 1 core biopsy will be snap frozen, and 1 core biopsy will be formalin fixed and paraffin embedded. Portions of tumors and normal tissue can then be prepared for further storage and analysis per laboratory guidelines. This will include placement of portions of tissue in aliquoted conical tubes in RPMI solution in TPS. The snap frozen specimens may be then stored for future investigation, including micro- and microdissection as well as for DNA/RNA extraction, and ultimately stored at -80ºC.
- Archival Tissue: If available, 1-2 paraffin embedded tissue blocks containing formalin-fixed tumor slides will be requested. Paraffin blocks may then be processed according to standard institutional protocol, with final preparation of 20 unstained slides for available analysis.
- All specimens will be delivered with the attached specimen submission form. All tissue will then be stored at the Hakimi Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY).

Peripheral Blood Sample Collection and Storage

Time Points: C1D1, C2D1, C3D1, , End of Treatment

Materials and Collection:

Materials§	C1D1*	C2D1 & C3D1	End of Treatment*
Vacutainer CPT Tubes (8mL/each tube)	X (3 tubes)	X (2 tube)	X (3 tubes)
Streck BCT Tube (10mL/each tube)	X (1 tube)	X (1 tube)	X (1 tube)
EDTA Tube (6cc/each tube)	X (1 tube)	X (1 tube)	X (1 tubes)

Table 1: Peripheral Blood Sample Schedule

*All blood draws should occur prior to avelumab administration. Collections may occur ±7 days of specified time point.
**An additional two blood draws at different time points beyond those listed is permitted when feasible based upon clinical / immunological findings
§Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Preparation:

Vacutainer CPT Tubes: The BD Vacutainer CPT Tube (Catalog: 362761), or equivalent, will be used. For collection, standard phlebotomy will fill tubes with 8 mL of blood, with attempt to obtain full 8 mL during collection attempt. The tube will then be inverted several times after collection to ensure adequate mixing. The patient's name, MRN, adhesive stickers will be attached to the tube. The date/time will be noted on the collection requisition form. The RSA will then deliver all specimens to Hakimi Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY).

Streck Tubes: The Streck Cell-Free DNA BCT tube (Streck Catalog No 218961), or equivalent, will be used. For collection, standard phlebotomy will fill each tube with 10 mL of blood, with attempt to obtain full 10 mL during collection attempt. The tube should be inverted several times after collection. The patient's name, MRN should be documented on adhesive stickers to each tube. The date/time will be noted on the requisition form, and the tubes will be placed in a biohazard bag at room temperature. The RSA will then deliver all specimens to Hakimi Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY).

EDTA Tubes: The BD lavender tube (BD Catalog: 367863) will be used. For collection, standard phlebotomy will fill each tube with 6 mL of blood, with attempt to obtain full 6 mL during collection attempt. The tube should be inverted several times after collection. The patient's name, MRN should be documented on adhesive stickers to each tube. The date/time will be noted on the requisition form, and the tubes will be placed in a biohazard bag at room temperature. The RSA will then deliver all specimens to Hakimi Lab at IPOP, MSKCC Zuckerman Research Center (417 East 68th Street, New York, NY). Samples may then be stored at -80ºC per standard practice procedure for future analysis.

Data Entry for Specimen Collection

MSKCC RSA and/or Chan laboratory personnel will collect information into a secured database once samples are collected and transported. If a sample is not fully collected, the reasoning for incomplete or partial collection should be documented into the database as well for accurate records.

<u>RNA/DNA Preparation Methodology</u>

Tumor samples will be prepared with the AllPrep DNA/RNA/Protein Mini Kit from Qiagen (CAT: 80004). Samples then will be used include fresh snap frozen core biopsies, biopsies preserved in RNA*later*, or alternatively paraffin embedded core biopsies. When samples are in paraffin embedded, the RN*easy* FFPE Kit and QIAamp DNA FFPE Tissue Kit will be used. Changes to the RNA/DNA preparation methodology may be adapted depending upon the most recent, generally accepted protocols.

Tumor Exome Sequencing and matched normal DNA from blood

Whole exome sequencing will be carried out using the Illumina Hiseq 2100 according to Nextera Rapid Capture kit (Cat # FC-140-1000) protocol with using 50 ng of genomic DNA as input. Nextera Rapid Capture kit targets 214,405 coding exons offering comprehensive coverage of human exomes with target size of 37 Mb. Changes to the methods for exome sequencing may be adapted depending upon the most recent, generally accepted protocols.

DNA Damage Responses will then be characterized using homologous recombination deficiency (HRD) assays which encompass multiple parameters. This may include loss of heterozygosity scoring (LOH), large scale transition scoring (LST), and telomeric allelic imbalance scoring (TAI).

Transcriptome Sequencing of Tumor RNA

Messenger RNA is isolated from Total RNA using the Life Technology Dynabeads mRNA Direct Microkit (Cat# 61021). The isolation relies on base pairing between the poly (A) residue at the 3' end of most mRNA, and the oligo (dt) 25 residues covalently coupled to the surface of the Dynabeads. Other RNA species lacking a poly (A) tail do not hybridize to the bead and are readily washed away. Briefly, 1 ug of RNA is heat denatured at 70°C and 50 ul of lysis/binding buffer and beads are added to bind the mRNA to the beads. Two rounds of mRNA isolation are performed and finally mRNA is eluted in 10 ul of nuclease free water. The resulting isolated mRNA contains low ribosomal RNA content, which allows for most accurate measurement of coding transcripts.

The mRNA is subsequently converted to representative cDNA libraries for strand-specific RNA sequencing on the Ion Torrent Personal Genome Machine (PGM) system using the Life Technology Ion Total RNA –Seq kit (Cat #4475936). Briefly, 1-500 ng of mRNA is fragmented with RNAse III enzyme and purified using beads. The size of the fragmented RNA is assessed on the Agilent 2100 Bioanalyzer. The fragmented RNA is hybridized and ligated with Ion adapters and subsequently reverse transcribed using SuperScript III to generate single stranded cDNA copies of the fragmented RNA molecule. Library generation uses a magnetic bead-based, size selection process, to enrich library fragments with 200-bp length. Complementary DNA library is subsequently amplified using Ion PCR primers, and Platinum PCR High Fidelity enzyme as per the protocol. The size and yield of the resultant amplified cDNA library size is determined on the Agilent High sensitivity DNA Bioanalyzer chip.

The library dilution factor is determined for the template preparation. Template preparation is carried out on OneTouch Emulsion PCR system using the Life Technology Ion PGM Template OT2 200 kit (Cat #4480285). OneTouch uses membrane passages and microfluidics to create

bulk emulsion of DNA library in oil and performs an *in situ* thermocycling PCR to produce template beads. The template beads are enriched on OneTouch ES using streptavidin beads to bind to biotinylated, properly adapted library fragments. This emulsion PCR and enrichment yields a sequencing template bead population where 95% of beads carry the template. The template beads are deposited on to the sequencing chip and sequenced on PGM using the Ion PGM Sequencing 200 Kit (Cat # 4482006) from Life Technologies. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Specific Pathways of interest that will be included for analysis include DDR pathways: *BRCA1, BRCA2, PARP1, ATM, ATR, RAD51C, BAP1, PALB2, MRE11, BARD1/BRIP1, RAD50/51/51B/51D, ERCC2, ERCC3, ERCC4, ERCC5, MMR* genes*, POLE, FANCC, FANCA, BLM, CHEK1, CHEK2, RB1, ATRX, as well as others.*

Somatic Mutation Identification and Verification

Matched tumor and normal exome sequencing reads will be mapped to the human reference genomic using Bowtie2. Non-uniquely mapped reads are then discarded, and calculation of mismatch statistics for each position is performed for both samples. The aligned reads are then trimmed at the 5' and 3' end at the points where the mismatch rate goes above 1% based on this analysis. To reduce bias introduced through PCR amplification during library preparation, multiple reads with alignments starting at the same genomic location with their consensus are replaced. MuTect, which is one of the methods used in the TCGA project to call somatic mutations, is then used to predict somatic variants single nucleotide variants (SNVs) from matched tumor and normal aligned reads. Haplotype inference over called SNV genotypes is performed using the RefHap Single Individual Haplotyping algorithm that uses read evidence to phase blocks of proximal SNVs.

RNA-Seq reads are mapped on a diploid human transcript library derived from the NCBI CCDS (http://www.ncbi.nlm.nih.gov/CCDS/CcdsBrowse.cgi) annotations. Expressed genes are identified by inferring gene expression levels from the RNA-Seq aligned reads, using IsoEM. IsoEM is an accurate EM algorithm that makes use of information such as insert size, quality scores, and read pairing, if available, to handle read mapping ambiguities. Epitope prediction is done for somatic SNVs that appear in expressed genes, according to FPKM (Fragment per Kilobase Per Million reads) values predicted by IsoEM.

After the candidate neo-epitope peptides are selected, the SNVs encoding these peptides will be verified by reverse-transcriptase PCR followed by DNA sequencing. Two sets of primers are synthesized for each SNV with the second set of primers as nested primers. RNA will be extract from each tumor sample using Qiagen RNAeasy Mini Kit. The first primer set will be used to synthesize cDNA samples from RNA samples. The cDNA will be used as template for reverse transcriptase PCR reaction using the second set of primers. The PCR product will be purified using QIAquick PCR Purification Kit. Purified PCR product and the second primer set will be used to Genewiz to sequence verify the SNVs called by high throughput sequencing analysis. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Neo-Antigen Prediction

For each somatic SNV in the expressed gene, reference and mutated peptide sequences are then generated based on the two inferred haplotypes for each CCDS transcript. Generated amino acid sequences are then processed using the NetMHC epitope prediction program and scored using an Artificial Neural Network (ANN) algorithm, for the patients' identified HLA alleles. The Differential Agretopic Index (DAI), which is the difference between the NetMHC score for the mutated peptide and its un-mutated wild type counterpart, is calculated for each peptide, by subtracting the wild type score from the mutant score. Epitopes based on DAI will be ranked. Multiple mutational antigen prediction scores (Net MHC, DAI, pathogen-associated sequences) may be compared in an exploratory fashion and each will be tested against response rates. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

MSK-IMPACT Analysis

MSK-IMPACT will be performed according to the institutional protocol. This assay analyzes a pre-defined set of cancer susceptibility genes which are captured and sequenced on an Illumina HiSeq™. Tumor mutational burden will be calculated using the total number of non-synonymous mutations divided by the total genomic target region for which mutations are reported. TMB will be reported as an estimate / mB of DNA. Copy number assessment will be used to determine gene amplification or deletion (amplification defined as >2-fold change, deletion defined as <2-fold change). Degree of copy number change is influenced by tumor purity and content. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Immune Infiltrate Analysis

The immune infiltrate analysis will be performed using several techniques, including IHC, immunofluorescence, flow cytometry and/or computational approaches (deconvolution) based upon RNA sequencing data analysis. Matrix type analysis will be performed including CIBERSORT and single-sample gene expression set analysis (ssGSEA). Populations of cells analyzed may include, but will not be limited to CD4, CD8, Treg populations, B cells, MDSC, monocytes, and dendritic cells and expression of biologically relevant/phenotypic markers thereof. Standard established institutional protocols will be applied. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Peripheral blood analysis

Peripheral blood analysis will be performed using flow cytometry, and/or computational approaches including immune deconvolution based upon RNA sequencing data analysis. Populations of cells that may be characterized include, but are not limited to, CD4, CD8, Treg populations, B cells, MDSC, monocytes, and dendritic cells and expression of biologically relevant/phenotypic markers thereof. Standard established institutional protocols will be applied. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Peripheral blood analysis will also include analysis for circulating tumor DNA (ctDNA). Tumor DNA will be extracted using QIAamp circulating nucleic acid kit, and libraries will then be prepared

using previously described and captured gene specific DNA probes. This may include gene sets as described by MSK-ACCESS, as well as targeted amplification for select genes of interest in RCC. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Metabolomic Profiling

Tissue samples will be identified for metabolite changes with metabolite identification and quantification. Snap frozen core biopsy samples will be incubated and prepared to precipitate polar metabolite proteins for mass spectrometer analysis per standard procedures. Non-targeted gas and liquid chromatography coupled with mass spectrometer (LC/MS) analyses will then be performed, with lower limit of quantitation of 100 ng/g of tumor. Metabolites of interes t may include, but is not limited to, specific TCA cycle metabolites: fumarate, succinate, malate, alpha-ketoglutarate, citrate, isocitrate, malate, fumarate, glutamine, glutamate, ATP, 2-HG, aspartic acid, asparagine, orotic acid. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.