MSK PROTOCOL COVER SHEET

A Phase Ib/II Study of Talazoparib and Axitinib in Metastatic Renal Cell Carcinoma

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

The introduction of targeted vascular endothelial growth factor inhibitors (VEGFR TKIs) and immune checkpoint blockade (anti-PD-1/PD-L1, CTLA-4) has transformed the management of patients with advanced renal cell carcinoma (RCC). Despite this success, many patients ultimately progress through approved combination or monotherapy standards, and novel strategies are desperately needed. Utilizing shared features amongst RCC tumor subtypes, including an upregulation of angiogenesis and increased intrinsic genomic instability, combining DNA repair blockade with anti-angiogenesis agents may enhance the clinical effect in patients with advanced RCC.

A unifying feature of clear cell RCC remains the almost uniform functional loss of the von Hippel-Lindau (*VHL)* gene, and subsequent upregulation of hypoxia-inducible factor (HIF) directed pathways, including downstream upregulation of vascular endothelial growth factor (VEGF). Targeting VEGF is the main mechanism of action of several FDA-approved agents including sunitinib and axitinib. Many studies have also elucidated that *VHL*-loss further drives genomic instability, and most clear cell RCC tumors harbor abnormal DNA repair mutational signatures. As tumor hypoxia also induces genomic instability, the addition of a PARP inhibitor which selectively blocks DNA repair may further promote DNA damage, genomic instability, and cancer cell death.

Based on the above rationales, we propose a single-center, open label, phase Ib/II clinical trial to evaluate the combination of the VEGFR TKI axitinib and a selective PARP inhibitor, talazoparib, in patients with refractory advanced clear cell RCC. In the phase Ib dose escalation, the primary objective is to identify the maximum tolerated dose (MTD) of talazoparib in combination with standard dose axitinib. In the phase II dose expansion, the primary objective is to evaluate efficacy as measured by objective response rate by RECIST v1.1 criteria, with secondary objectives including progression-free survival, overall survival, and safety and tolerability of combination therapy. Exploratory objectives will include tissue analyses characterizing gene expression profiles for angiogenesis and genomic studies to identify correlates for response to combination therapy.

In the study design, patients will be initially enrolled in a 3+3 dose escalation across 3 pre-determined dose levels, with 3-6 patients at each talazoparib dose level (0.5 mg daily, 0.75 mg daily, 1 mg daily) based upon previously established RP2D dosing for talazoparib monotherapy and combination therapies (NCT02326844, NCT03330405) (Figure 1). As we do not expect overlapping drug toxicities between these study medications, axitinib will be administered at standard of care dosing (5 mg BID) with options for dose adjustment as clinically indicated. Both talazoparib and axitinib will be administered concurrently in 28-day cycles with clinical assessments for dose-limiting toxicity (DLT) evaluations at each dose level according to CTCAE v5.0.

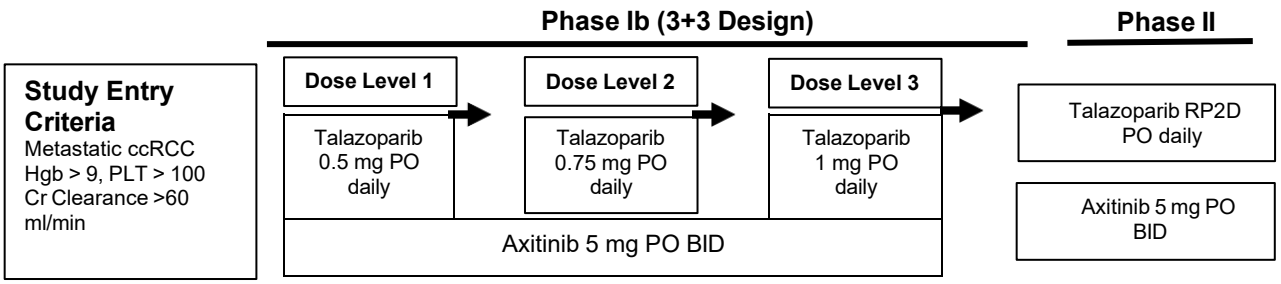


Figure 1: Clinical Trial Schema: ccRCC=clear cell RCC, Hgb=hemoglobin g/dL, PLT=platelet 10^9/L, Cr=creatinine

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Phase Ib Primary Objectives:

1. Identify the recommended dose of talazoparib in combination with standard-dose axitinib in previously treated metastatic clear cell RCC patients.

Phase Ib Primary Endpoint:

1. Dose-limiting toxicity, as defined in Section 4.2, based on adverse events classified according to CTCAE v5.0 observed over 1 cycle of combination talazoparib and axitinib.

Phase II Primary Objective:

1. Evaluate the efficacy as measured by objective response rate (ORR) of combination talazoparib and axitinib in previously treated metastatic clear cell RCC patients.

Phase II Primary Endpoint:

1. ORR of combination talazoparib and axitinib by RECIST v1.1 (defined in Section 13.1).

Phase II Secondary Objectives:

1. Evaluate the progression-free survival (PFS) of combination talazoparib and axitinib in the total cohort (defined in Section 13.1)
2. Evaluate the overall survival (OS) of combination talazoparib and axitinib in the total cohort (defined in Section 13.1).
3. Evaluate the safety and tolerability as defined by occurrence of Grade 3 or higher adverse events for combination talazoparib and axitinib by CTCAE v5.0 criteria throughout the entire treatment period (defined in Section 13.1 and Appendix 2).

Phase I/II Exploratory Objectives:

1. Characterize genomic instability of RCC tumors through assessment of DNA damage response (DDR) and homologous recombination deficiency (HRD) and correlate with response to the combination of talazoparib and axitinib on pre-treatment archival tissue.
2. Characterize angiogenesis and inflammatory signatures by gene expression profiling and correlate with response to the combination of talazoparib and axitinib on pre-treatment archival tissue and peripheral blood samples.

3.0 BACKGROUND AND RATIONALE

3.1 Renal Cell Carcinoma Overview

Renal cell carcinoma (RCC) remains the most common and lethal form of kidney cancer, affecting over 65,000 patients in the United States each year with a rising incidence (*1*). The growing incidence of RCC likely stems from modifiable risk factors including tobacco use, hypertension, obesity, as well as a shift in incidental radiographic diagnoses in asymptomatic patients (*2*). As one-third of patients with RCC

present with *de-novo* metastatic disease, and one-fourth of patients experience disease relapse, there remains a high unmet need for systemic therapy options for patients with advanced disease.

Large scale efforts using The Cancer Genome Atlas (TCGA) and the TRACERx study have helped uncover patterns within the context of clinical and tumor evolution, and have revealed a distinct genomic landscape for RCC pathophysiology (*3*-*5*). A hallmark event characterizing >90% of clear cell RCCs remains chromotripsis of chromosome 3p with subsequent *VHL* loss (*3*). Haploinsufficiency of *VHL* remains insufficient for tumor growth, and may also precede RCC development by event decades (*6*), and secondary genomic and/or epigenetic events affecting *VHL* and other chromatin remodeling genes remain central to disease pathogenesis. Functional loss of *VHL* leads to downstream accumulation of hypoxia inducible factor (HIF) transcriptional factors, leading to changes in cell proliferation, migration, metabolism, and importantly angiogenesis (*7*-*9*). This upregulation of angiogenesis has been the central focus of therapy options for patients with advanced disease, and has spurred development of several vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs).

3.2 Current Systemic Therapies for Advanced RCC

Over the past decade, there has been an evolving landscape of treatment options for patients with advanced RCC. This has mainly comprised of two separate drug classes: VEGFR TKI therapy and immune checkpoint inhibitors (ICIs). Prior to the immunotherapy era and for patients ineligible for ICI therapies, VEGFR TKI monotherapy was the standard frontline option for patients with advanced disease (*10*), and this has been used a reference gold-standard control for the most contemporary phase III studies employing ICI or combined VEGFR TKI plus ICI therapy (*11, 12*).

Over the past 2 years, three combination regimens (combination ICI plus ICI, and combination ICI + VEGF) have showed superiority to sunitinib monotherapy in the first-line setting (*12, 14, 15*). In the KEYNOTE-426 study, axitinib plus pembrolizumab showed an ORR of 59.3% and median PFS 15.1 months compared to patients in the sunitinib monotherapy group (ORR 35.7%, median PFS 11.1 months). Further, the 1-year OS probability was 89.9% for combination therapy compared to 78.3% in the sunitinib group, demonstrating a hazard ration of 0.53 (95% CI 0.38-0.74, p<0.0001). In the JAVELIN Renal-101 study, the ORR for the overall patients was 55.9% (95% CI 51.1-60.6%) compared to 30.2% for sunitinib monotherapy, with a median PFS of 12.5 months in the overall population versus 8.4 months. Lastly, in the CheckMate-214 study, combination ipilimumab plus nivolumab showed a superior ORR of 42% versus 27% (p<0.001) when compared to sunitinib monotherapy as well.

Sequencing of different VEGFR TKI therapy remains common for many patients, and retrospective results have shown that those patients who receive second-line VEGFR TKI therapy after first-line ICI treatment have similar efficacy without increased toxicity signals (*13*). This remains unclear for patients undergoing therapy in the first-line setting with VEGFR TKI plus ICI agents as the field continues to mature data. Many patients though exhaust this line of therapy and subsequently are treated with a subsequent VEGFR TKI monotherapy option, and whether other biological mechanisms can be targeted to improve efficacy remains unclear. Regarding efficacy in the second-line setting, prior studies evaluating single agent axitinib versus sorafenib in this setting (AXIS trial) have demonstrated an ORR 23% (*16*), and ICI monotherapy with nivolumab demonstrated an ORR of 25% in patients who were also previously treated with VEGFR TKI therapy.

3.3 DNA Damage Response (DDR) Pathways and Advanced RCC

DNA repair remains 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) (*17*). 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 (*18*) 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” (*19*). This has been exploited recently through PARP inhibition in patients with underlying *BRCA* germline mutations in multiple tissue models (*20-24*). Additionally, other DDR losses like MMR deficiency have been shown to have higher mutational load correlating with improved response to immune checkpoint blockade therapy (*25*).

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 (*26, 27*). Pre-clinical work highlights that *VHL*-loss also 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 (*28*). In addition, *VHL*-deficient RCC cells also show impaired nucleotide excision repair (NER) capacities as well (*29*).

BRCAness, the notion that DDR associated genes other than *BRCA1* and *BRCA2* confer similar defects in DNA repair, has increasingly been applied in many other tumor models and genes (*30*). 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

then re-analyzed 400 patients in the TCGA clear cell RCC cohort irrespective of tumor thrombus and identified high predominance of a *BRCAness* mutational signature (COSMIC-3), accounting for 74.25% of patients (297/400 samples) (*31*).

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 (*32*). Expression changes were confirmed upon TCGA interrogation, and *VH-* loss specifically was associated with impaired DNA DS break repair, conferring a *BRCAness* phenotype (*33*). Based on the above studies, this *BRCAness* phenotype is associated with a majority of clear cell RCCs and may render them susceptible to therapies which impact DNA repair.

3.4 PARPi Therapy Rationale for Advanced 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 (*34*).

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 (*23*). In total, the FDA has approved multiple agents across tumors in mostly *BRCA* mutant populations (Table 1), and further exploration of other DDR pathway mutants including those tumors with *BRCAness* remains underway. For instance, single-agent olaparib is currently undergoing evaluation in a single-center phase II study in renal cell carcinoma patients harboring inactivation mutations in DNA repair genes (ORCHID, NCT03786796).

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 1: FDA Approved PARPi in 2019: PARPi=PARP inhibitor; CR=complete response; PR=partial response

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 (*32*). There remains no preclinical data for combination PARPi therapies (with VEGFR TKI or immune checkpoint inhibitors) in renal cell carcinoma models.

3.5 Axitinib Clinical Experience in Advanced RCC Patients

Axitinib (AG-013736) is a selective, potent vascular endothelial growth factor receptor 1, 2, 3 blocker. Axitinib has been FDA approved since 2012 for the treatment of metastatic renal cell carcinoma after treatment with one prior line of systemic therapy and has been FDA-approved as of April 2019 for first-line treatment for patients with advanced RCC when combined with pembrolizumab or avelumab. Results from the AXIS (A4061032) study, a phase III study of axitinib versus sorafenib for patients with previously-treated advanced RCC, led to the FDA-approval in the refractory setting. In this trial, patients treated with axitinib (n=361) were found to have median PFS 6.7 months (95% CI 6.3-8.6), median OS 20.1 months (95% CI: 16.7-23.4) and ORR 19.4% (95% CI: 15.4-23.9) compared to sunitinib with median PFS 4.7 months (95% CI 4.6-5.6), median OS 19.2 months (95% CI: 17.5-22.3) and ORR 9.4% (95% CI: 6.6-12.9) (*16*).

Two randomized phase III studies evaluating the combination of axitinib with ICI therapy in the untreated advanced RCC setting reported in 2019. In the JAVELIN Renal 101, patients were randomized to axitinib plus avelumab (anti-PD-L1) versus sunitinib, and the co-primary endpoint met was improvement in median PFS (13.8 versus 7.2 months, HR: 0.61, p<0.001) in PD-L1 patients. The ORR and CR rate in PD-L1+ patients was 55% and 4% with combination treatment (*12*). In the second randomized phase III study of axitinib plus pembrolizumab versus sunitinib in untreated patients with advanced RCC, the trial met showed that combination therapy lowers risk of death (HR: 0.53, 95% CI 0.38-0.74, p<0.0001) and disease progression (HR: 0.69; 95% CI, 0.57–0.84; P< 0.001). The ORR was 59.3% (95% CI, 54.5–63.9) in the combination group and 35.7% (95% CI, 31.1 to 40.4) in the sunitinib group (P< 0.001) (*15*).

Axitinib has been combined with several therapeutics with manageable toxicity profiles in advanced RCC and other tumor types. Outside metastatic RCC tumor types, axitinib has been combined with chemotherapies (docetaxel, gemcitabine, paclitaxel, cisplatin/carboplatin, FOLFOX, pemetrexed, capecitabine), VEGF inhibitor bevacizumab. In patients with advanced RCC, phase I studies have been formed in combination with targeted agents including crizotinib (A40961068 protocol, ORR 6%, median PFS 5.6 months) (*36*). Given this pairing previously, axitinib is a favorable potent drug with demonstrated efficacy in the first and refractory settings, and pairs well as the VEGFR TKI therapy when combining with other therapies.

As of June 2018, 45 studies in total have evaluated the safety, efficacy and pharmacokinetics of axitinib including 15 phase I studies and 30 studies in patients with underlying cancer. The mean absolute oral bioavailability of the drug is 58%, with a ~2-fold increase in in patients with underlying hepatic impairment. For single-agent axitinib, 98% of subjects have reported at least one adverse event. The most common treatment-emergent AEs were diarrhea (55%), hypertension (51%), fatigue (47.1%), decreased appetite (40%), nausea (32.6%), weight decreased (32.2%), dysphonia (31.1%), palmar-plantar erythrodysesthesia (29.4%), hypothyroidism (22.6%), vomiting (22.6%), constipation (20.3%), proteinuria (20.0%). Grade ≥3 events occurred most frequently were: hypertension 20.7%, fatigue 10.2%, and diarrhea 10.1% (Axitinib, Pfizer Investigational Brochure 2018).

Regarding anti-angiogenic therapy, dynamic contrast enhanced MRI (DCE-MRI) have shown that axitinib treatment decreased the overall tumor blood flow / permeability as early as 2 days after initial treatment, with a maximum reduction on Day 7 after dosing. These changes have also been correlated in decreased micro vessel density and cellular viability. Neo-angiogenesis may occur after drug withdrawal and tumors remain fully re-vascularized within 7 days in one pre-clinical study, suggestive that continuous daily dosing for axitinib may be optimal for angiogenesis blockade.

3.6 Talazoparib Clinical Experience Summary

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 (*37*).

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 (*22*). 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 2).

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	0	0

Table 2: 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 (*22*))

3.7 Rationale for Combination Talazoparib and Axitinib Therapy

Although the tumor mutational burden of RCC remains modest, specific mutational signature analyses have identified that RCC tumors specifically may harbor defects in DNA DS break repair which supports sensitivity to PARPi (Section 3.4). In line with this, RCC cells have shown sensitivity to PARPi olaparib and talazoparib (*32*). Furthermore, *VHL*-loss, a unifying feature of clear cell RCCs, confers increased DNA replication fork stalling and stress. Other RCC variants harboring secondary genomic alterations known to portend to aggressive clinical courses have also showed sensitivity to the PARPi olaparib (*35*).

Tumor and tissue hypoxia itself also leads to suppression of DNA repair through both HIF-dependent and independent mechanisms, with suppression of multiple repair pathways including *BRCA*1/2 (*38*). This notion has led to the concept of “contextual” synthetic lethality, and pre-clinical models have identified that cells have significantly increased sensitivity to PARP inhibition in hypoxic microenvironments (*39*). As potent VEGFR TKIs remain capable of inducing site-specific tumor hypoxia, pairing a potent VEGFR TKI (axitinib) with a selective PARPi (talazoparib), may lead to improved clinical outcomes when compared to historical controls of VEGFR TKI monotherapy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-center, non-randomized, open-label phase Ib/II study to evaluate the safety, tolerability and preliminary efficacy of combination talazoparib and axitinib in patients with previously treated, advanced clear cell RCC. The phase Ib will enroll patients in a 3+3 dose-escalation across 3 defined

dose levels, and the phase II dose expansion will enroll patients in a Simon two-stage design with treatment at the recommended phase II dose (RP2D) of talazoparib in combination with standard-dose axitinib established for preliminary efficacy analysis.

4.2 Intervention

4.2.1 Phase Ib Dose Escalation

In the phase Ib dose escalation portion of the study, 3 dose levels (dose level 1-3) will be explored, starting with dose level 1 to assess for potential dose-limiting toxicity (DLT; for definitions see section 4.3) and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). The dose levels are summarized in table 3: both drugs are self-administered on a continuous schedule; axitinib will be given at the same starting dose across all dose levels, while talazoparib doses will be increased level-to-level (0.5 mg, 0.75 mg, and 1 mg daily). Treatment will be discontinued for progression of disease, as defined by RECIST v1.1 (Section 13.2).

Dose Level	Talazoparib Dose	Axitinib Dose	Number of Patients
1	0.5 mg PO daily	5 mg PO BID	3-6 patients
2	0.75 mg PO daily	5 mg PO BID	3-6 patients
3	1 mg PO daily	5 mg PO BID	3-6 patients

Table 3: Dose Level in the Phase Ib dose escalation

After a minimum of 3 patients per dose level have completed DLT evaluation period of >28 days, an escalation to the next dose level or addition of 3 patients to the current dose level will be performed based upon the following dose escalation criteria:

1. If there are no DLTs, dose escalation to the subsequent dose level may proceed
2. If 1 of 3 patients experiences a DLT, 3 additional patients may be enrolled at that current dose level. If there are no further DLTs in those 3 additional patients, dose escalation to the next dose level may proceed.
3. If a DLT occurs in ≥2 patients in any dose level of 3-6 patients, no further dose escalation will occur. If the lower dose level only enrolled 3 patients prior to escalation, an additional 3 participants will then be added to that dose level for a total of 6 evaluable patients.

Those patients who do not meet the minimum exposure criterion (75% of cycle 1 of talazoparib and axitinib; see also Biostatistics Section 14.1) due to treatment-related adverse events will be counted as a DLT. Those patients who fail to meet the minimum exposure criterion unrelated to study agents will be considered ineligible for DLT assessment and must be replaced for the phase Ib study to meet its primary objective of safety assessment.

Patients who experience a DLT at any dose level may continue therapy at a reduced dose level per the discretion of treating physician but will not be counted for further DLT assessments at that reduced dose level. They will be followed for toxicity and safety as outlined in this protocol. Patient enrolled at any dose

level (including those above MTD) who are tolerating treatment may continue to receive additional doses of talazoparib plus axitinib at that dose level, even after MTD determination.

4.2.2 Phase II Dose Expansion

Once the MTD has been determined based on the above, integrating safety and efficacy signals observed during the DLT period and beyond, a RP2D will be chosen by the study team and will be applied during the expansion portion of the trial. The RP2D may be the same or be at a lower dose level than the MTD, but will not exceed the MTD. This phase II dose expansion will then open to further evaluate safety, tolerability and preliminary efficacy of combination therapy. This part 2 will include 6 patients from the dose escalation phase and will continue to enroll up to 25 patients at the RP2D in a Simon two-stage manner. All patients enrolled in this part will receive talazoparib at the RP2D to be taken PO daily, and starting dose axitinib to be taken at 5 mg BID. Dose modification of each drug will be done per protocol (See Section 10.3 for talazoparib dose modification, and 10.4 for axitinib dose modification). All patients will then undergo radiographic tumor assessments as scheduled to assess for response to combination therapy. Treatment with this combination of study agents will be continued until DLT toxicity or disease progression.

The opening of the dose expansion part of this study will be based upon evaluation of safety and tolerability of combination therapy during phase Ib. A continuous safety monitoring rule will be used to continuously evaluate safety and tolerability, and accrual will be paused if excessive DLTs are seen (see Biostatistics Section 14.0 for plan).

All patients will undergo follow up visits with both short-term and long-term following their last dose of talazoparib and axitinib, and will begin follow up for progression of disease and patient survival.

4.3 Dose-Limiting Toxicity (DLT) Definitions and Assessments

A DLT will be defined as any of the following events that are considered definitively, possibly or probably related to talazoparib as listed below. In the phase Ib dose-escalation, this event will be considered a DLT only during the first 28 days of combination treatment with the purpose of dose determination for further development. In the phase II dose expansion, a DLT will also be considered throughout the remainder of the treatment period for patients who have completed 28 days of therapy to help understand longer term tolerability of the regimen. The maximally tolerated dose (MTD) will be defined as the highest dose level with 0-1 DLT in 6 patients.

DLT events include:

1. Non-hematologic adverse event grade 3 or higher except for grade 3 or higher amylase, lipase in the absence of clinical symptoms, and grade 3 nausea/vomiting or diarrhea in the absence of appropriate prophylaxis.
2. Grade 3 thrombocytopenia with associated bleeding
3. Grade 4 anemia or thrombocytopenia
4. Grade 4 neutropenia with fever

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.1 Axitinib Drug Information and Storage

Axitinib (AG-013736) drug will be supplied by the study funder Pfizer for all patients. Drug will be supplied in a dosing container which will contain a sufficient drug amount of reach treatment period including overage. There are four strengths of tablets that will be acceptable (1 mg, 3 mg, 5 mg and 7 mg), and all tablets will be packaged in appropriate material and stored at room temperature (15-30ºC, 59-86ºF) or per the approved label. The research staff will inform patients on the proper storage requirements for the take home investigational drug. Further information regarding axitinib handling is listed in the investigational brochure. Any excursions from the product label storage conditions will be reported upon discovery. Deviations from these requirements should be documented and reported. Once an excursion is identified, the investigational product should be quarantined and not used until Pfizer provides permission for use of the investigational product.

Axitinib is self-administered orally twice daily (PO BID) on a continuous schedule during days 1-28 of the treatment cycle. Axitinib should be dosed at the same time, and if a dose is missed, it may be taken up to 4 hours after scheduled time. Patients should not take more than two doses within a 24-hour period, and if any doses are missed in the cycle, they will not be made up. Missed doses should be recorded as missing in the patient's diary (Appendix 4). 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 axitinib orally with or without food. The definitive food effect study (A4061053) conducted in healthy volunteers has shown no clinically significant changes in axitinib plasma exposure or Cmax in the presence of food compared with a fasting state (Axitinib IB, 2018). Patients should be instructed to take axitinib swallowed whole with a glass of water. If vomiting occurs after axitinib is swallowed, the dose itself should only be replaced if intact tablets are seen and counted.

The dose of axitinib may be adjusted per clinical guidelines (detailed in Section 10.4). The use of study medication at doses exceeding levels specified in this protocol will be considered an overdose. There is no known antidote in the event of a patient overdose, and the treatment for adverse events should be aimed at treating the underlying symptoms.

5.2 Talazoparib Drug Information and Storage

Talazoparib (BMN-673) will be supplied by trial funder Pfizer for all patients. 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 4 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 (detailed in Appendix 4). The reason for the missed dose should be recorded in the diary for study personnel to review. The patient should then 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.

The dose of talazoparib may be adjusted per guidelines (detailed in Section 10.3). 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.

5.3 Treatment Interruptions and Delays

Talazoparib may be maximally interrupted for 28 consecutive days. Axitinib may be maximally interrupted for 28 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.

5.4 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 and axitinib should 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. The medication pill diary (detailed in Appendix 4) will be reviewed with the patients by the study team.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

1. Biopsy proven metastatic or unresectable renal cell carcinoma with clear cell component
2. Prior treatment with at least 1 VEGFR TKI and 1 PD-1/PD-L1 immune checkpoint inhibitor (ICI). Combination VEGFR TKI plus ICI will be counted as 1 line of therapy. During the dose escalation portion of the study prior TKI exposure is not required.
3. Dose escalation portion: No maximum prior lines of therapy. Dose expansion portion: maximum of two prior lines of therapy.
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

4. Adequate Renal Function ≥ 60 ml/min according to the Cockcroft-Gault formula
   (1) Patients with moderate renal impairment (creatinine clearance 30-59 ml/min by Cockcroft-Gault) may be eligible in the phase II dose expansion (see Section 6.1.2)
5. Adequate Hepatic Function including:
   a. Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
   b. AST ≤ 3 x upper limit of normal (ULN) without liver metastasis
   c. ALT ≤ 3 x upper limit of normal (ULN) without liver metastasis
   d. AST or ALT ≤ 5 x upper limit of normal (ULN) for patients with liver metastasis
   e. Patients with known Gilbert's syndrome may be included if total bilirubin ≤ x 3 ULN
6. Eastern Cooperative Group (ECOG) Performance Status 0-2. (defined in Appendix 1)
7. Patients must have measurable disease by RECIST v1.1 (defined in Section 13.2). At least one measurable lesion should not have been previously irradiated.
8. Women of childbearing potential must have negative serum pregnancy testing at screening. All women will be considered childbearing potential unless meeting criteria including:
   a. 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.
   b. Documented hysterectomy or bilateral oophorectomy surgery
   c. Medically confirmed ovarian failure
   d. 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 women, and 4 months for men. See Section 6.3 for additional detail.
9. Recovery of baseline CTCAE v5.0 grade ≤1 toxicities related to prior study treatments unless adverse events are clinically non-significant per investigator's discretion and/or stable on supportive therapy if needed.
10. 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.

6.1.1 Participant Inclusion Criteria for Phase II Dose Expansion

1. Maximum 2 lines of prior therapy. Combination VEGFR TKI plus ICI therapy will be accepted as 1 line of therapy.
2. Adequate Renal Function ≥ 30 ml/min according to the Cockcroft-Gault formula.
   a. Patients with normal renal function (Cr clearance ≥ 60 ml/min by Cockcroft-Gault formula) will receive talazoparib at RP2D.
   b. Patients with moderate renal impairment (Cr clearance 30-59 ml/min by Cockcroft-Gault formula) will receive talazoparib at one dose level lower than RP2D.

6.2 Participant Exclusion Criteria

1. Prior treatment with talazoparib or other agents which target PARP
2. Prior treatment with axitinib. Other VEGFR TKIs are permissible.
3. Patients < 18 years old
4. 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 study (7 months after last dose of the study treatment for women, and 4 months for men)
5. Prior diagnosis of myelodysplastic syndrome (MDS) or diagnosis of other malignancy that requires anti-cancer directed therapy within the last 12 months. Exclusions include those cancers that are considered cured by local therapy (e.g. 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).
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.
7. Significant vascular disease (i.e. aortic aneurysm requiring surgical repair, recent arterial thrombosis) within 6 months prior to first dose of therapy.
8. Ejection Fraction (EF) ≤50% by echocardiogram (ECHO). Multi-gated acquisition scan (MUGA) should be obtained to estimate EF if quality of ECHO is insufficient.
9. Uncontrolled hypertension defined as systolic blood pressure (BP) ≥160 mmHg or diastolic BP ≥100 mmHg despite anti-HTN therapy.
10. Evidence of bleeding diathesis or significant unexplained coagulopathy (i.e. absent of anticoagulation)
11. Clinical signs or symptoms of gastrointestinal obstruction requirement parenteral hydration, parenteral nutrition, or feeding tube.
12. Uncontrolled effusion management (pleural effusion, pericardial effusion, or ascites) which requires recurrent drainage procedures.
13. Active infection requiring parenteral antibiotic therapy.
14. 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.
15. Known hypersensitivity to talazoparib or axitinib, or any component in formulations.
16. Severe acute or chronic medical conditions which may significantly increase the risk of study participants, per treating investigator’s discretion.
17. Radiation therapy to any site (including bone) <2 weeks prior to the first dose of therapy.
18. Symptomatic brain metastasis or leptomeningeal disease requiring steroid use. Patients are eligible if they are neurologically stable for 4 weeks, 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.
19. Current or anticipated use of potent P-gp inhibitors within 7 days prior to randomization or anticipated use during the study (Appendix 3).
20. Inability to swallow capsules, known intolerance to talazoparib and axitinib or its excipients, known malabsorption syndrome, or other conditions which impair intestinal absorption.

6.3. Teratogenic Risk of Combination Therapy

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

Study team personnel including investigators and clinical nursing staff should confirm with the patient and their partner that they have selected 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.

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.

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 axitinib 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 patient, and questions will be answered by the treating investigator before written consent is obtained.

7.1 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 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).

7.2 Randomization

N/A as this study does not include randomization.

8.0 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.

9.0 PRE-TREATMENT/INTERVENTION

1. History and Physical Assessment
2. Vital Signs
3. Eastern Cooperative Group (ECOG) Performance Score
4. Toxicity Assessment via CTCAE v5.0
5. Assessment of concomitant medications and medication reconciliation
6. 12-lead electrocardiogram
7. Echocardiogram
8. Optional pre-treatment biopsy
9. Radiographic tumor assessment of chest, abdomen, and pelvis
10. Radiographic brain imaging if clinically indicated
11. Bone scan if clinically indicated (technetium-99m (99mTc)-methylene diphosphonate (MDP) scan per MSK standards)
12. Confirmation of tissue availability:

(1) Availability of archival tissue should 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, and 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) Thyroid Function Testing (TSH, Free T3 and Free T4)
    (5) Serum Pregnancy Testing for women of childbearing potential
    (6) Urinalysis including TP urine, random and random creatinine for UPCR ratio
    (7) Screening for hepatitis B: HBV surface antigen, HBV core antibody, with HBV PCR performed reflexively if abnormal results

10.0 TREATMENT/INTERVENTION PLAN

10.1 Combination Talazoparib and Axitinib Drug Administration

Talazoparib will be administered at the assigned dose level to be taken PO daily and axitinib will be administered at 5 mg PO BID starting on Cycle 1 Day 1. Talazoparib and axitinib administration do not have to be coordinated in a particular fashion; both can be taken together or separate, in either order. Both medications will be continued until DLT toxicity or confirmed disease progression. Patients will continue both medications for a 28-day cycle.

10.2 Medication Compliance

A medication dosing diary will be given to the patient to aid in patient compliance and dosing instructions (see Appendix 4). The diary will be maintained by the patient and will include entry items for the patients to include information regarding taken, missed, or changed axitinib and 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.

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.

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

10.3 Talazoparib Dose Modifications

During the phase Ib, the dose escalation phase will start with dose level 1 and will continue as defined in Section 4.2. If a DLT is experienced, patient may resume treatment at a reduced dose level per the treating investigator's discretion with dose reductions as outlined below (Table 4). Patients should not re-escalate to prior dose levels if dose-reduced for DLT.

Talazoparib Dose Alteration			
Dose Modification	Dose Level 1	Dose Level 2	Dose Level 3
Starting Dose Level	0.5 mg PO daily	0.75 mg PO daily	1 mg PO daily
First Dose Reduction	0.25 mg PO daily	0.5 mg PO daily	0.75 mg PO daily
Second Dose Reduction		0.25 mg PO daily	0.5 mg PO daily
Third Dose Reduction			0.25 mg PO daily

Table 4: Talazoparib Dose Reduction Schema

During the dose escalation, patients will be required per eligibility to have adequate renal function of ≥60 ml/min. During the dose expansion, adjustment of the starting dose per renal function will be mandatory. Patients with creatinine clearance ≥60 ml/min will be started at RP2D, and those patients with moderate renal impairment as defined by creatinine clearance 30-59 ml/min by Cockcroft-Gault will be started at one dose level reduction from the RP2D per the above schema (Table 4). Patients will creatine clearance <30 ml/min will not be eligible for either phase Ib dose escalation or dose expansion.

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 require permanent discontinuation of talazoparib may continue axitinib monotherapy at the discretion of the investigator.

10.4 Axitinib Dose Modifications

During the phase Ib dose escalation and phase II dose expansion, at the discretion of the investigator, management of adverse events including hypertension, venous or arterial thromboembolic events, hemorrhage, gastric perforation, gastric fistula, and proteinuria may require temporary dose interruption or permanent discontinuation and/or dose reduction of axitinib. Guidance for adverse event management related to axitinib is provided in Section 11.2. If a dose reduction is required, patients will be treated at a reduced 3 mg PO BID as a first dose reduction, and 2 mg PO BID as a second dose reduction (Table 5). Patients who are unable to tolerate 2 mg BID of axitinib should have axitinib discontinued permanently.

Asymptomatic changes in ejection fraction or congestive heart failure have been previously documented with VEGFR TKI therapy, and therefore, investigators may consider holding or reducing the dose of axitinib as clinically indicated. In the event of a grade ≥3 cardiac related toxicity, if it is deemed at the investigator's discretion to be related to axitinib, axitinib should be discontinued permanently. Patients who require permanent discontinuation of axitinib may continue talazoparib monotherapy at the discretion of the investigator.

In accordance with the existing FDA label, patients who tolerate axitinib for at least 4 consecutive weeks with no axitinib related adverse reactions of grade >2 (according to NCI CTCAE v5.0), no dose reductions

to axitinib, and stable BP <150/90 mm Hg on ≤2 concurrent anti-hypertensive medications, may have their dose increased from 5 mg BID to 7 mg BID, and subsequently from 7 mg BID to 10 mg BID using the same criteria (Table 5) after demonstrating tolerability for at least 28 days. Patients participating in Part 1 of the study should not have their dose level of axitinib increased before study day 29 (C2D1). Patients should not have axitinib dose increased if talazoparib has been dose modified within the prior 28 days. Patients should not have axitinib doses exceeding 10 mg BID at any time point during the study. Lastly, in the event that subsequent to completion of RP2 dose determination a new safety signal is apparent in RP2 patients whose axitinib is dose escalated >5mg BID, dose-increases beyond axitinib 5mg BID will not be permitted in subsequent participants. All RP2 patients previously dose escalated beyond 5mg BID should at that point be considered for axitinib dose reduction to 5mg BID.

Axitinib Dose Level	Dose
D+2	10 mg BID
D+1	7 mg BID
Starting Dose	5 mg BID
D-1	3 mg BID
D-2	2 mg BID

Table 5: Axitinib Dose Modification Levels. BID = twice daily dosing.

10.5 Combination Therapy Dose Modifications

In the event of a planned dose reduction, patients should hold the drug that is being reduced 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. during a treatment cycle. In such cases lower-strength capsules or tablets will be dispensed mid-cycle, rather than delaying re-initiation of therapy at lower dose. Left-over capsules or tablets at the prior strength will be returned to the study team at the next scheduled Day 1 clinic visit. Once the talazoparib or axitinib dose has been reduced, 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 for talazoparib but is permissible for axitinib.

If talazoparib is held for > 28 consecutive days, it should be permanently discontinued. If axitinib 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, re-initiation must be discussed with and approved by the study PI.

10.6 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 the medical record from screening visit to 30 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.

10.6.1 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. Bone modifying agents (including bisphosphonates and RANKL 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 it can be provided safely and effectively. This includes:
    1. Low molecular weight heparin (LMWH) is allowed if the patient has no evidence of untreated brain metastases and has had no complications from thromboembolic event on the anticoagulation regimen. Oral anticoagulants including warfarin, coumadin-related agents, direct thrombin or direct factor Xa inhibitors are not permitted.
    (1) 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.
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.
5. Caution and monitoring for potential increased adverse events should be used upon concomitant use of the following CYP3A4/5 Inhibitors as this may affect axitinib: ketoconzale, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin. If co-administration of a strong inhibitor is required, a dose decrease of axitinib by half should be recommended.
6. Caution and monitoring for potential increased adverse events should be used upon concomitant use of the following CYP3A4/5 Inducers: rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital. If a strong inducer is required, a dose adjustment of axitinib is recommended.

10.6.2 Prohibited Therapy

2. Any other anti-cancer therapy (chemotherapy, biological therapy, immunotherapy, vitamins used as cancer therapies) other than talazoparib and axitinib.
3. Any other investigational agents other than talazoparib or axitinib for anti-cancer or non-cancer related therapy.
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
5. Oral anticoagulants including warfarin, coumadin-related agents, direct thrombin or direct factor Xa inhibitors.
6. EPO stimulating agents: i.e. erythropoietin alpha, darbepoetin alfa,
7. TPO stimulating agents: i.e. romiplostim, eltrombopag, thrombopoietin

10.7 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.

10.8 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.

10.9 Hypercalcemia Management

Bisphosphonate or denosumab therapy can be administered as per local 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.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

11.1 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 11.6)

11.2 Treatment Period

All activities during treatment period have been detailed under the Schedule of Activities (Section 11.6) 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.

11.3 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, Appendix 2), 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 assessment at screening, focused physical assessments as indicated during follow-ups) prior to study treatment administration.

All patients will require a baseline ECG and ECHO, and on-treatment ECGs or ECHOs should be performed as clinically indicated. Clinically significant findings on subsequent ECGs or ECHOs 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 (Section 11.6). The required safety testing should be reviewed prior to study drug administration on Days 1 (Table 6). Blood chemistry and hematologic assessment must be performed at baseline, prior to each talazoparib and axitinib dose, end of treatment visit, and 30 days post-treatment for safety follow up. For female patients of childbearing potential, serum pregnancy testing must be performed at baseline and at least every month during treatment. Thyroid function testing (Free T4, Free T3, TSH) should be performed at baseline, and at least every 8 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)
Urinalysis	Urine dipstick for urine protein – if positive, collect microscopic reflex testing. Urine dipstick for blood – if positive, collect microscopic reflex testing. Total protein (random) and creatinine (random) for UPCR ratio.
Pregnancy Testing	For female patients of childbearing potential, serum testing with a sensitivity of at least 25 mIU/mL.

Table 6: 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 UPCR=urine protein/creatinine ratio.

11.4 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.

11.5 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 should also undergo baseline brain MRI or contrast enhanced brain CT at screening if clinically indicated. 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. Brain imaging with MRI or CT will only be performed when clinically indicated or 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 56 weeks of study drug therapy. After 56 weeks, 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 RECIST v1.1. Date of progression will be determined for progression-free survival analysis in secondary endpoint review. 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.

11.6 Schedule of Activities

Activity	Screening	Cycle 1		Cycle 2-3+				Follow-Up	
	≤28 days	C1 D1	C1 D15	C2 D1	C2 D15	C3+ D1	End of Treatment (EOT)	Short Term	Long Term
Visit Window		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 30 days	± 7 days	± 14 days
Informed Consent[1]	X								
Medical History[2]	X								
Pathology Review[3]	X								
Optional Tissue Biopsy[4]	X								
Height[5]	X								
Physical Assessments[5]	X	X	X	X	X	X	X	X	
Vital Signs[5]	X	X	X	X	X	X	X	X	
ECOG Performance Status[6]	X	X	X	X	X	X	X	X	
Hematology[7]	X	X	X	X	X	X	X	X	

[1]Informed consent must be obtained within 28 days prior to C1D1 and prior to any study specific procedures.
[2]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 history, and concomitant medication use.
[3]Confirmation of existing documentation of renal cell carcinoma histology through a specialized genitourinary pathology review at Memorial Sloan Kettering Cancer Center.
[4]Patients may undergo an optional screening tumor biopsy of primary or metastatic site. Collection details are noted in protocol lab manual.
[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]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. Serum LDH is checked at baseline.

Chemistry[7]	X	X	X	X	X	X	X	X	
Amylase, Lipase, Total Protein[7]	X	Perform as clinically indicated							
LDH[7]	X	Perform as clinically indicated							
Urinalysis[8]	X	Perform as clinically indicated							
Serum Pregnancy Test[9]	X	X		X		X		X	
Hepatitis B Serology Testing[10]	X								
Thyroid Function Testing[11]	X					X	X		
Research Blood Testing[12]		X		X		X	X		
12-lead ECG[13]	X	Perform as clinically indicated							
ECHO[14]	X	Perform as clinically indicated							
Talazoparib[15]		Continuous							
Axitinib[16]		Continuous							

[8]Urine dipstick for urine protein – if positive, collect microscopic reflex testing. Urine dipstick for blood – if positive, collect microscopic reflex testing. At Screening, Total Protein Urine Random and Creatinine Random Urine should be collected in addition to urine dipstick.

[9]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 and monitoring (Sections 6.2, 6.3, 11.4)

[10]HBV surface antigen, HBV core antibody, with HBV PCR performed reflexively if abnormal results.

[11]TSH, Free T4, Free T3 will be checked at Screening and every 8 weeks from C3D1 for safety monitoring. EOT thyroid testing will only be performed if >8 weeks from prior testing.

[12] Research Blood Tests will be collected on Day 1 of Cycle 1-3, and at EOT and post-treatment visit. Blood tests will be acceptable within 7-day window.

[13]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.

[14]ECHO scans to assess ejection fraction. MUGA can be performed to estimate ejection fraction if quality of ECHO is insufficient for measurement. Cardiac evaluation (i.e. ECG, ECHO) may be performed clinically indicated.

[15]Talazoparib will be taken continuously orally daily.

[16]Axitinib will be taken continuously orally twice daily.

Tumor Assessments[17]	**X**	Perform every 8 weeks for 56 weeks, then every 12 weeks thereafter until disease progression (±7 days)							
Baseline Brain and Bone Scan[18]	Perform as clinically indicated.								
Toxicity Assessments[19]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Survival[20]									**X**

[17]Assessments will be performed using RECIST v1.1 criteria by CT chest/abdomen/pelvis or CT chest with MRI abdomen/pelvis. Baseline imaging is to be performed within 28 days of first dose of study treatment. Imaging should be performed with contrast agents unless strictly contraindicated for medical reasons. Timing of disease reassessment 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 treating investigator.

[18]Baseline brain MRI or CT and bone scan should be performed within 28 days of first dose of study treatment if clinically indicated by treating physician. Repeat assessment should be performed whenever disease progression is suspected per treating investigator.

[19]Toxicity Assessments will be assessed by CTCAE v5.0 criteria (Appendix 2).

[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.

11.6 Severity Assessments

All patients will be assessed for toxicity per National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (Appendix 2). This assessment will include the maximum intensity of adverse events (AEs). If the event is serious, the CTCAE grade must be documented and be consistent with the description of the CTCAE grade in the narrative section of the serious adverse event (SAE) report. CTCAE grading will be graded with a numerical score 1-5 associated with the unique clinical descriptions for each severity. The general guideline for this grading scheme as it relates to the severity of AE is listed below (Table 7):

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 7: CTCAE v5.0 General Grading Guidelines

11.7 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 CTCAE (v5.0, Appendix 2).

11.7.1 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:

1. **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
2. **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.

11.7.2 Adverse Event Follow-Up

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.

11.8 Pregnancy and Fertility Assessments

Pregnancy testing is required at screening and recommended monthly until the end of the trial. Serum or urine pregnancy testing should be performed at screening and at the end of the study. Urine or 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.

11.9 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 or DLT, requires reporting to Pfizer within 2 business days.

11.10 Talazoparib Toxicity

11.10.1 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 (Table 8).

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**	**Axitinib**
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.	Consider hold of axitinib and reinitiate axitinib 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.	Consider hold axitinib and reinitiate axitinib once toxicity Grade ≤1 or baseline. Permanently discontinue axitinib if the same Grade 3 toxicity recurs if talazoparib had already been discontinued and recurrent event occurs on axitinib 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 be resumed at the reduced dose level.	Consider hold axitinib and reinitiate axitinib once toxicity Grade ≤1 or baseline. Permanently discontinue axitinib if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on axitinib only).

Table 8: Dose Modification Guide for Hematologic Toxicity for Talazoparib and Axitinib

11.10.2 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 (Table 9).

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 9: Dose Modification Guide for Non-Hematologic Toxicity for Talazoparib and Axitinib

11.10.3 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 (Table 9).

11.11 Axitinib Related Toxicities

11.12 Axitinib Related Cardiac Toxicity

In clinical studies with axitinib for the treatment of metastatic RCC, cardiac failure events (including failure, congestive failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 12/672 patients (1.8%). Grade 3/4 cardiac failure events were reported in 7/672 patients (1%), and fatal events have been reported in 2/672 patients (0.3%). Patients should be monitored periodically for signs or symptoms related to cardiac failure during therapy, and appropriately managed with investigation (e.g. EKG, ECHO) as indicated. Development of event may require temporary interruption, discontinuation or dose modification of axitinib as per clinical practice.

11.13 Axitinib Related Hypertension

In pooled clinical analyses of patients treated with axitinib for metastatic RCC, hypertension was reported in 344/672 patients (51%) receiving axitinib. Grade 3 hypertension was reported in 148/672 patients (22%) receiving axitinib. Grade 4 hypertension was reported in 7/672 patients (1%) receiving axitinib. The median onset time for hypertension was within the first month of starting axitinib therapy and has been observed as early as 4 days after starting axitinib. Blood pressure should be well-controlled prior to initiating therapy, and patients should be monitored periodically during treatment for development and/or worsening of hypertension and treated as needed with anti-hypertensive therapies per standard practice. If persistent hypertension continues despite anti-hypertensive drug regimens, axitinib dose should be reduced. For those patients who have axitinib treatment interrupted or discontinued, patients who are receiving anti-hypertensives should be monitored for hypotension.

11.14 Axitinib Related Thyroid Dysfunction

In pooled clinical analyses of patients treated with axitinib for metastatic RCC, hypothyroidism was reported in 165/672 (25%). Hyperthyroidism was reported in 11/672 patients (2%). Therefore, monitoring thyroid function before treatment initiation, and monitoring of thyroid function during treatment has been required per study protocol. Treatment of hypothyroidism or hyperthyroidism should be treated per standard medical practice to maintain a euthyroid state.

11.15 Axitinib Related Arterial / Venous Thromboembolism

In pooled clinical analyses of patients treated with axitinib for metastatic RCC, arterial thromboembolic events were reported in 19/672 (3%), with grade 3 and 4 events reported in 1% and 1% of patients, respectively.

Regarding venous thromboembolic events, events have been reported in 19/672 (3%) of patients receiving axitinib, with grade 3 VTE events in 1%.

11.16 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.

12.0 CRITERIA FOR REMOVAL FROM STUDY

12.1 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 and axitinib 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.

12.2 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 should 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.

12.3 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 (PD) by RECIST v1.1. or patients who are no longer experiencing clinical benefit as determined by investigator should be discontinued from study treatment.
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 (7 months for women, 4 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 adverse events.

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

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Calculated Study Endpoints

1. Maximally Tolerated Dose (MTD): highest dose level with 0-1 DLT in 6 patients
2. Objective Response Rate (ORR): proportion of patients with confirmed complete response (CR) or partial response (PR) assessed by RECIST v1.1, relative to the total population of patients enrolled who initiate combination therapy.
3. Progression-free Survival (PFS): duration of time from start of treatment until death or progression of disease. 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.

4. 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.
5. Safety and Tolerability: proportion of patients who have developed a grade ≥3 adverse events.

13.2 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 RECIST v1.1.

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.

At radiographic tumor assessment, patients will then be evaluated for response per RECIST v1.1 (Table 10). Complete Response (CR) must be confirmed with repeat imaging 6 weeks later.

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.

Table 10: RECIST v1.1 Criteria for Response Guidelines

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.

13.4 Correlative Research Plan

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

For specimen preparation and transportation: For archival tissue, 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. All specimens will be delivered with a 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 samples will be collected at Day 1 of Cycles 1-3, and at the End of Treatment visit (Table 11). Collection may occur ±7 days of specified time point, and an additional two blood draws at different time points beyond those listed is permitted when feasible based upon clinical findings. All peripheral blood specimens will be delivered with a specimen submission form, and stored to the 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.

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

Table 11: Peripheral Blood Sample Schedule. *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 findings. §Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

For exploratory objective 1, analyses will focus on characterizing genomic instability of RCC tumors through assessment of DNA Damage Response (DDR) and homologous recombination deficiency (HRD) with subsequent correlation with response to the combination of talazoparib and axitinib. For this aim, tissue whole exome sequencing will be performed 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. A Cox proportional hazards regression model will be used for this analysis.

For exploratory objective 2, analyses will focus on characterizing angiogenesis and inflammatory signatures by gene expression profiling and subsequent correlation with response to the combination of talazoparib and axitinib. Using pre-treatment specimens, gene expression profiling will be performed to identify angiogenesis-high/low, and immune infiltrated-high/low tumors. Peripheral blood will also be analyzed for circulating markers of angiogenesis and PARP activity. Further stratification of angiogenesis tumors by standard scoring metrics to cluster these 4 groups, and correlations will then be performed for analysis (Section 14.3).

14.0 BIOSTATISTICS

14.1 Phase Ib Biostatistics

The primary objective of the phase Ib dose escalation is to determine the recommended dose of talazoparib for combination with axitinib as determined by the MTD. The phase Ib portion of the trial will require between 4 and 18 patients in a 3+3 dose escalation design across three planned separate dose levels. The DLT window is 29 days and patients will initially be enrolled in dose level 1 (see Table 3).

The MTD will be defined as the dose level at which a dose limiting toxicity (DLT) occurs in at most 1 out of 6 patients in that dose levels. CTCAE v5.0 will be used for toxicity evaluation, with specific DLTs as outlined in Section 4.2. The safety assessments will be reported based upon frequency of adverse events (overall, SAE, DLTs) and the frequency of clinically meaningful laboratory values. Other safety data will be summarized as changes from baseline while on therapy and will reported as a frequency.

In this phase Ib dose escalation phase, all patients must meet the minimum exposure criterion to be considered evaluable for primary endpoint analysis. The minimum exposure criterion includes any patient who takes at least 75% of the planned dose for both talazoparib and axitinib during the first 29 days. Patients who do not experience a DLT in the first 29 days who meet the minimum exposure criterion will be considered to have enough safety data to conclude that a DLT has not occurred. Those patients who do not meet the minimum exposure criterion due adverse events related to talazoparib will be counted as a DLT. Those patients who fail to meet the minimum exposure criterion unrelated to study agents will be replaced for primary endpoint analysis in this dose escalation phase.

DLTs will be listed according to dose level. All patients who receive at least 1 dose of combination treatment will be evaluated for safety. Separately by dose level, AEs will be summarized as number of patients according to CTCAE term and grade, where grade is the maximum across a patient's treatment period.

The table below (Table 12) provides the probability of dose escalation given various true DLT rates; there is a high probability (0.71) of dose escalation if there truly is a 20% DLT rate, and a low probability (0.17) of dose escalation if there truly is a 50% DLT rate.

	True Probability of DLT at Current Dose						
	0.10	0.20	0.30	0.40	0.50	0.60	0.70
Probability that dose is escalated	0.91	0.71	0.49	0.31	0.17	0.08	0.03

Table 12: Probability of Dose Escalation in phase Ib

Dose Level 3 patients were treated with 1 mg Talazoparib QD PO + 5 mg Axitinib BID PO. Out of the six total patients enrolled on this dose cohort, 1/6 had a lack of exposure to minimum of 75% of Talazoparib and Axitinib on Cycle #1 due to toxicities. Given that this patient did not meet this minimum exposure criterion possibly related to drug, this was counted as a DLT. In review of the total cohort, 20% of patients had a dose reduction of talazoparib and axitinib in this cohort (DL-3).

Given this experience of the total 6 patients on Dose Level #3 including review of the compliance, dose reduction and toxicities encountered, as well as the experience of the prior Dose Levels #1-2 (0.5 mg and 0.75 mg Talazoparib, respectively), we have concluded that the maximum tolerated dose (MTD) is 1 mg Talazoparib PO daily and the RP2D is 1 mg Talazoparib PO daily when combined with 5 mg Axitinib 5 mg BID PO.

The study will continue into the dose expansion phase to further evaluate the safety, tolerability, and preliminary efficacy of combination therapy. Newly accrued patients will enroll at the 1 mg Talazoparib PO Daily and 5 mg Axitinib PO

14.2 Phase II Biostatistics

The primary objective of the phase II dose expansion is to evaluate the efficacy of combination therapy as measured by objective response rate (ORR). Subsequent to determination of the recommended phase 2 dose (RP2D) during Part 1 of the trial the dose expansion phase will continue to enroll patients at that dose level to a total of 25 patients treated at the RP2D. This dose expansion cohort will include those patients treated at the RP2D during the part I dose expansion.

The phase II dose expansion cohort will be an optimal Simon two-stage design, with the first stage accruing a total of 14 patients. If 4 or more of those patients have a response to therapy, the study will continue for a total enrollment of 25 patients at the RP2D. If 3 or less patients have a response in the first 14 patients, the phase II will be terminated early for futility. If 8 or more of the 25 patients have a response to combination treatment, the study will be deemed a success. This two-stage design discriminates response rates between 20% and 45% and offers 90% power and type I error rate of 10%. The historical control of 20% was chosen based upon prior studies evaluating monotherapy axitinib in the second line setting (*16*), as well as other randomized phase II/III studies evaluating other second line agents including monotherapy cabozantinib and monotherapy nivolumab, which have response rates between 17-20% (*40, 41*). Further, the upper bound of 45% remains in line with current first-line standards of care options for patients as novel agents used in this setting demonstrate ORR of 42%-59% in the first-line setting (Section 3.2). The probability of early termination of the phase II portion under the null is 70%. At the end of the study, ORR will be calculated with 90% two-sided confidence interval (corresponding to the one-sided α=0.10 in the statistical design).

Patients will be considered evaluable for the primary endpoint if they have received at least 1 dose of each study agent. All patients who receive at least 1 dose of each study agent will be considered evaluable for safety analyses.

In secondary analyses, we will estimate PFS and OS using Kaplan-Meier method and report median values with confidence intervals. Further, AEs will be summarized as number (%) of patients according to CTCAE term and grade, where grade is the maximum across a patient's treatment period. The number (%) of patients who experience at least 1 grade 3-5 AE will be reported with 90% CI.

A continuous safety monitoring model will be used to continuously assess for toxicity in the phase II dose expansion (Table 13). Sequential boundaries will be used to monitor dose-limiting toxicity rate in the phase II dose expansion. The accrual will be paused if excessive numbers of DLTs are seen, that is, if the number of DLTs is equal to or exceeds the allowable boundary as defined in the table below. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary to be at most 20% when the rate of dose-limiting toxicity is equal to the acceptable rate 30%. This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.3, using a one-sided level 0.083808 test. The trial will be paused if the number of dose limiting toxicities is equal to or exceeds the boundary, b_n out of n patients with completed follow-up. At that point, study termination should be considered; alternatively, if deemed appropriate and safe the trial may be resumed with subsequent patients enrolling at the next lower dose level. Dose reductions for other patients already on therapy should be considered at that point.

Number of Patients, *n*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Boundary, b_n	-	-	3	3	4	4	5	5	6	6	6	7	7	8	8	8	9	9	10	10
Number of Patients, *n*	**21**	**22**	**23**	**24**	**25**															
Boundary, b_n	10	11	11	11	12															

Table 13: Continuous Safety Monitoring Model for Phase II Enrollment

14.3 Exploratory Analyses

Due to the limited sample size, all analyses will be descriptive and graphical. For all continuous measurements used in biomarker analysis, summary statistics (i.e. mean, standard deviation, median, percent of coefficient of variation, and minimum/maximum levels) will be calculated at baseline as appropriate based on patient's available samples. For discrete measurement biomarkers (e.g. tumor marker status), frequencies and percentages of categorical biomarker measures will be determined at baseline including deleterious DNA damage response (DDR) status, tumor mutational burden (continuous), and clusters for angiogenesis-high/low, immune-infiltrate-high/low. We will graphically examine the relationship between the biomarkers and measures of efficacy, such as ORR and PFS. 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. A volcano plot may be constructed to demonstrate significantly differentiated expressed genes when comparing response (PD vs. CR/PR) to combination talazoparib and axitinib therapy.

14.4 Study Accrual / Feasibility

The total anticipated cohort that is needed to complete the dose escalation phase Ib portion of will be 12-18 patients. The total anticipated cohort size for the second part of the trial (the phase II dose expansion, essentially) is 25 patients at RP2D, and this total will include 6 patients enrolled in part I at the RP2D and 19 patients from part II. Therefore, the anticipated maximum accrual for both parts 1 and parts 2 is 37 patients. The anticipated accrual for both the phase Ib/II is 2.5 years. This is based upon historic accrual patterns for early and late-phase phase II and phase III clear cell RCC trials, which would account for all patients in this trial. In a previous pre-treated clear-cell RCC phase II trial at MSKCC, the accrual has

been 95 patients from 2016-2019 (3 patients / month). As this clinical study accrues for patients pre-treated in the 2nd-4th line setting, and excludes patients previously treated with axitinib which has now moved to the first-line setting, we anticipate a slower accrual to this clinical trial (1-2 pts/month). Therefore, we expect full accrual over 2 years with subsequent follow-up over 1 year to complete a 3-year total study.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

15.1 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 substantial disruption 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

15.2. External SAE Reporting

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.

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 substantial disruption 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.

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.

15.3 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. An SAE report must be completed for any event where doubt exists regarding its seriousness.

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.

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 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/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

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.

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.

16.2 Data Management

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.

16.3 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.

16.4 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.

16.5 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.

16.6 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).

16.7 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

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18.0 APPENDICES

Appendix 1: ECOG Performance Status

Appendix 2: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Appendix 3: Prohibited Potent P-gp Inhibitors

Appendix 4: Patient Pill Diary

Appendix 1: ECOG Performance Status

The ECOG scale is used to assess a patient's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the patient.

Grade	ECOG
0	Fully active, able to care on pre-disease performance without restriction
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and to keep level of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. He cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 2: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

See:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 3: 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