Official Protocol Title:	A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety o f Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426)
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TITLE:

A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426)

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.1 8.7 8.8	Statistical Analysis Plan Summary Interim Analyses Multiplicity	1) Revised assumptions on control arm median PFS and OS. 2) Revised IA1 trigger from 50% final OS events to once achieving 305 PFS events and 7 months of minimum follow up. 3) Added one interim analysis for PFS. 4) Initial alpha to PFS and OS changed from 0.1% and 2.4% to 0.2% and 2.3% respectively.	1) The revised assumptions for median PFS and OS on the control arm are based on emerging data (see Section 8.9). 2) The trigger for IA1 based on achieving a minimum of 305 PFS events and 7 months minimum follow up allows relatively mature PFS data and the timing is more predictable while the accrual of OS events is less predictable due to expected confounding factors. 3) Addition of PFS IA is to have earlier chance of observing positive efficacy of PFS with relatively mature data. 4) Slightly higher alpha is reallocated to PFS to ensure adequate power for this important primary endpoint without compromising the power of OS.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	The estimated duration of the trial was revised to 44 months.	To align with changes to the SAP.
1.0	Trial Summary	Added additional text to the following paragraph: 'After study treatment has been discontinued, AEs will be collected for 30 days from the last dose "or until new anti-cancer therapy is initiated, whichever is earlier"..; serious adverse events (SAEs) will be collected for … if the subject initiates a new anti-cancer therapy "prior to completing 90 days of follow-up"…	To be consistent with other sections.
2.1	Trial Design	The 3rd to last paragraph starting with "This trial will use a group-sequential design that includes…" is revised based on the updated statistical design and analysis from 8.1, 8.7, and 8.8	See rationale provided in the Primary Reason for Amendment Table above.
3.2	Secondary objectives	Added new Objective (2): To evaluate PFS rate per RECIST 1.1 as assessed by BICR at 12, 18, and 24 months based on data adequacy; to evaluate OS rates at 12, 18, and 24 months based on data adequacy.	Since study is evaluating a novel combination including immunotherapy, landmark analyses on PFS and OS are important to compare and characterize the tail of the curve.
4.3	Benefit / risk	The first sentence of the first paragraph is updated based on current pembrolizumab approved indications and exposures in clinical trials.	Self-explanatory.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.2.2	Dose Modification	Table 6, for the irAE management with corticosteroid and/or other therapies for hypothyroidism, "liothyroinine" corrected to "liothyronine".	Typographical error correction.
5.5.1.1	Caution Use of Inhibitors and Inducers of CYP Enzymes (Axitinib)	Added text indicating grapefruit or grapefruit juice increases axitinib plasma concentrations and should be avoided.	Added per axitinib label
6.1	Trial Flow Chart (Pembrolizumab in Combination with Axitinib)	Footnote m and Footnote u- added text to read that KPS and safety labs would be collected at every cycle visit, starting from Cycle 2.	Typographical error correction to be consistent with the Trial Flow Chart entries.
6.1, 6.2 2.1	Trial Flow Chart (Pembrolizumab in Combination With Axitinib) and Trial Flow Chart (Sunitinib) Trial Design	Footnote q in both flow charts –added text in italics to the final sentence, now it reads: Bone scans must be performed for the confirmation of Complete Response (CR) *for subjects with a positive bone scan at baseline*. In Section 2.1 8th paragraph, sentence also updated to clarify that bone scan for CR confirmation is only required for subjects with baseline positive bone scan.	To clarify that for confirmation of Complete Response (CR), bone scan is only required for subjects who had positive bone scan at baseline.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.3	Trial Flow Chart Second Course Phase (Retreatment)	Hematology, Chemistry laboratory tests and KPS are collected at every cycle. Thyroid and urinalysis will continue to be collected at every other cycle, starting at Cycle 2, at treatment discontinuation and 30 days after discontinuation. No footnote changes are needed.	Protocol requires that chemistry and hematology laboratory test results need to be available prior to each pembrolizumab dosing. This change clarifies that these are the only safety laboratory tests that need to be performed at each cycle visit during Second course phase. KPS is also added to have a complete safety assessment at each visit. INR is not required for every cycle visit as only pembrolizumab is administered at Second course phase.
7.1.2.7.2	Tumor Imaging During the Trial	In the last sentence of the last paragraph, text in italics was added, now it reads: Bone scans must also be performed for the confirmation of a CR *for those subjects who have a positive bone scan at baseline*.	See rationale for changes in 6.1 and 6.2 footnote q.
7.1.2.7.6	irRECIST Assessment of Disease	In Figure 4, timing of 3-5 business days for BICR email notice has been removed, now it reads: …YES = BICR provides email notice of verification of PD.	The timing for BICR email notice can only be approximated within 3 to 5 business days therefore the actual timeframe is removed.
7.1.4.3	Calibration of Equipment	The word 'critical' has been removed from the title; bullets and text after the first paragraph are removed.	It is investigator and site's responsibility for calibration and maintenance of study/trial equipment, which has already been stated in the first paragraph.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.2.3.3	Protocol-Specific Exceptions to Serious Adverse Event Reporting	In the first sentence of the first paragraph, "The Sponsor" has been changed to "The eDMC", hence the new first sentence reads: "The eDMC will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial."	Even though this is an open-label randomized study, the Sponsor will not look at the unblinded aggregated efficacy/ safety data until primary endpoints have been achieved or study has been concluded.
8.4.1.2	Secondary	For definition of disease control rate, SD has been changed to SD of ≥ 6 months.	This is a clinically meaningful SD.
8.5.2	Safety Analysis Population	Deleted the last sentence: "Details on the approach to handling missing data for safety analyses are provided in Section 8.6.2 Statistical Methods for Safety Analysis.	The sentence is no longer needed.
8.6.1.1	Progression-free Survival	Added the estimation for landmark PFS rates. Updated the censoring rules for primary and sensitivity analyses of PFS.	To provide the statistical method for the added secondary objective on landmark PFS rates. To be aligned with the recent changes in the therapeutic standard PFS censoring rules; the primary analysis closely follows FDA guidance; and the first sensitivity analysis closely follows the "intent-to-treat (ITT) complete follow-up principle".
8.6.1.2	Overall Survival	Added the estimation for landmark OS rates.	To provide the statistical method for the added secondary objective on landmark OS rates.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.6.1.4	Duration of Response	Updated the censoring rules for primary and sensitivity analyses of DOR.	To be aligned with the updated censoring rule for PFS.
8.6.1.6	Summary of Statistical Methods for efficacy	This is a new section header added after the first paragraph of previous section 8.6.1.5. In Table 18, header of the last column is changed from "missing data approach" to "missing data / censoring approach	The header was inserted to clarify the purpose for the table.
8.6.2	Statistical Methods for Safety Analyses	Updated the criterion for Tier 2 safety events and updated the list of additional events to be considered as Tier 2 or Tier 3 safety events.	Subjects enrolled in this study usually experience various adverse events of similar types, adverse events reported less frequent than in 10% or SAE, Grade 3-5 events reported in less than 5% of subjects would obscure the assessment of overall safety profile and add little to meaningful interpretation.
8.7	Interim Analyses	Editorial changes in Table 20.	To be more aligned with text in Section 8.7 and 8.8.
8.9	Sample Size and Power Calculations	Power statement is updated for PFS and OS endpoints.	Power statement has been changed using actual number of randomized subjects with updated median assumptions in the control arm based on emerging data.
8.10	Subgroup Analyses and Effect of Baseline Factors	Pre-specified each subgroup category and provided source where PD-L1 cutpoint has been selected.	To be more specific and clear.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase III trial of pembrolizumab plus axitinib vs. sunitinib monotherapy in advanced/metastatic renal cell carcinoma (mRCC)
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	Phase III
Clinical Indication	Treatment of subjects with advanced/mRCC
Trial Type	Interventional
Type of control	Active control
Route of administration	Intravenous, oral
Trial Blinding	Unblinded Open-label
Treatment Groups	• Pembrolizumab 200 mg every 3 weeks (Q3W) in combination with axitinib 5 mg twice daily (BID) • Sunitinib 50 mg once daily (QD) for 4 weeks and then off treatment for 2 weeks
Number of trial subjects	Approximately 840 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 44 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the informed consent form (ICF) through the final protocol-specified contact. After a screening period of ≤ 28 days, each eligible subject will first be stratified by the following two factors: 1) International mRCC Database Consortium (IMDC) risk categories (favorable vs. intermediate vs. poor) and 2) geographic regions (North America vs. Western Europe vs. "Rest of the World"). After stratification, subjects will be randomized 1:1 to one of two treatment arms: Arm 1) pembrolizumab in combination with axitinib or Arm 2) sunitinib monotherapy. Study treatments will continue until progressive disease (PD) is verified by blinded independent central review (BICR) or further confirmed by the investigator, unacceptable adverse events (AEs) or intercurrent illness prevents further administration of treatment, death or withdrawal of consent. For the pembrolizumab plus axitinib arm, pembrolizumab will be administered for a maximum of 35 doses (approximately 2 years). If a subject remains progression-free after 35 doses of pembrolizumab, treatment with axitinib will be continued as monotherapy until PD is BICR verified or further confirmed by the investigator. In addition, if 1 of the 2 compounds needs to be discontinued because of toxicity or intolerance, treatment with the other compound as monotherapy will be continued until PD is BICR verified or further confirmed by the investigator. Subjects who stop pembrolizumab after 35 doses without PD or stop pembrolizumab due to having achieved a complete response (CR) may be eligible for a second course of pembrolizumab treatment for up to 17 additional doses (approximately 1 year) upon experiencing PD. For both arms, in the event that a CR has been observed in a subject, study treatment may be discontinued at the discretion of the investigator after CR has been confirmed and after a minimum of 8 cycles (~ 24 weeks) of treatment with pembrolizumab plus axitinib or 4 cycles (~ 24 weeks) of treatment with sunitinib.

	After study treatment has been discontinued, AEs will be collected for 30 days from the last dose or until new anti-cancer therapy is initiated, whichever is earlier; serious adverse events (SAEs) will be collected for 90 days after the last dose of study treatment or for 30 days after the last dose of study treatment if the subject initiates a new anti-cancer therapy prior to completing 90 days of follow up, whichever is earlier. Subjects who discontinue study treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol defined schedule until: 1) PD is BICR verified or further confirmed by the investigator, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion or early termination, whichever occurs first. Following verification or confirmation of PD, all subjects will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.6.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase III randomized, open-label, multicenter, global trial to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for advanced/metastatic renal cell carcinoma (mRCC). The trial will be conducted in conformance with Good Clinical Practices (GCP).

The study includes 2 primary objectives: 1) to compare progression-free survival (PFS) between the 2 treatment arms per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [1] as assessed by blinded independent central imaging review (BICR) and 2) to compare overall survival (OS) between the 2 treatment arms. Key secondary objectives include comparison of objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) per RECIST 1.1 as assessed by BICR, patient reported outcomes (PROs), and safety and tolerability between the two treatment arms. See Section 3 for a complete description of study objectives.

Approximately 840 subjects will be enrolled into the study. Subjects must have measurable disease at baseline as assessed by the investigator/site radiologist per RECIST 1.1 and must provide an adequate tumor tissue sample in order to be eligible. See Section 5 for a complete list of study inclusion/exclusion criteria.

After a screening period of a maximum of 28 days, eligible subjects will first be stratified by the following 2 factors: 1) the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) [2, 3] and 2) geographic region (North America versus Western Europe versus "Rest of the World"). Subjects will then be randomized 1:1 into 1 of the following 2 treatment arms:

> **Arm 1)** combination of pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W) and axitinib 5 mg twice daily (BID) taken orally continuously or
>
> **Arm 2)** sunitinib monotherapy 50 mg daily (QD) taken orally for 4 weeks then off treatment for 2 weeks.

Study treatments will continue until progressive disease (PD) is BICR-verified or further confirmed by the investigator, unacceptable adverse events (AEs) or intercurrent illness prevents further administration of treatment, death or withdrawal of consent. When a subject is first identified with PD by the investigator, the site will request PD to be verified by BICR. Subjects who are clinically stable may continue treatment while waiting for BICR verification. Progressive disease status may be further confirmed by subsequent scans at the site. Detailed descriptions of imaging-based disease assessments, PD verification by BICR, and PD confirmation at the site are provided in Section 7.1.2.7.2 and Section 7.1.2.7.6.

For the combination arm, pembrolizumab will be administered for a maximum of 35 doses. If a subject remains progression-free after 35 doses of pembrolizumab, treatment with axitinib will be continued as monotherapy until PD is verified by BICR or further confirmed by the investigator. In addition, if 1 of the 2 compounds needs to be discontinued because of toxicity or intolerance, treatment with the other compound as monotherapy will be continued until PD is verified by BICR or further confirmed by the investigator. For both arms, in the event that a complete response (CR) has been observed in a subject, study treatment may be discontinued at the discretion of the investigator after the CR has been confirmed and after a minimum of 8 cycles of treatment (~24 weeks) in the pembrolizumab plus axitinib arm or 4 cycles of treatment (~24 weeks) in the sunitinib arm have been received. Detailed criteria for study treatment discontinuation and re-treatment are described in Section 5.8.

During the treatment period, subjects will have routine clinical visits for administration of or obtaining study treatment, monitoring safety and well-being, and assessing changes in disease status. Key study safety assessments include physical examinations, vital signs, electrocardiography (ECG), hematology and chemistry laboratories, thyroid function testing and urinalysis. At each visit, AEs and serious adverse events (SAEs) will be evaluated and graded per the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0. The doses of study treatment may be interrupted, reduced (only applicable for axitinib and sunitinib), or discontinued upon experiencing severe AEs in accordance with the dose modification guidelines for each study treatment (see Section 5.2.2 for details).

Study-scheduled imaging assessments for disease status include computed tomography (CT) and/or magnetic resonance imaging (MRI) for chest, abdomen, and pelvis. These imaging assessments will be performed at baseline, after randomization at Week 12, then every 6 weeks (Q6W) until Week 54, and every 12 weeks (Q12W) thereafter. Bone scans will be performed for all subjects at baseline. If a subject has a positive bone scan at baseline, bone

scans after randomization will be performed at Weeks 18, 30, 42, and 54, and then every 24 weeks (Q24W) thereafter. In addition, a bone scan is also required for confirmation of CR for subjects with a positive bone scan at baseline. Additional images for baseline and follow-up may be required if lesions outside the aforementioned regions are identified. See Sections 7.1.2.7.1 and 7.1.2.7.2 for details.

Imaging assessments will be performed according to the aforementioned schedule regardless of study treatment status until PD is BICR verified or further confirmed by the investigator, initiation of another anti-cancer therapy, death, or withdrawal of consent. Subjects who discontinue study treatment for reasons other than BICR-verified PD should continue with imaging assessments per the protocol-defined schedule until PD is BICR-verified or further confirmed by the investigator, initiation of a new anti-cancer treatment, death, withdrawal of consent, or study conclusion or early termination, whichever occurs first.

When a subject is first identified with PD by the investigator, the site will request PD to be verified by BICR. Subjects who are clinically stable may continue treatment while waiting for BICR verification. Progressive disease status may be further confirmed by subsequent scans at the site. Detailed descriptions of imaging-based disease assessments, PD verification by BICR, and PD confirmation at the site are provided in Section 7.1.2.7.2 and Section 7.1.2.7.6. Confirmation scans for CR or partial response (PR) will be performed at the next scheduled imaging assessment. All disease assessment imaging scans must be submitted promptly for BICR review.

After verification or confirmation of PD, subjects may initiate any subsequent anti-cancer treatment at the discretion of the treating physician and the subject per local standard of care. Pembrolizumab will not be provided to subjects who progressed on the sunitinib arm. All subjects will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

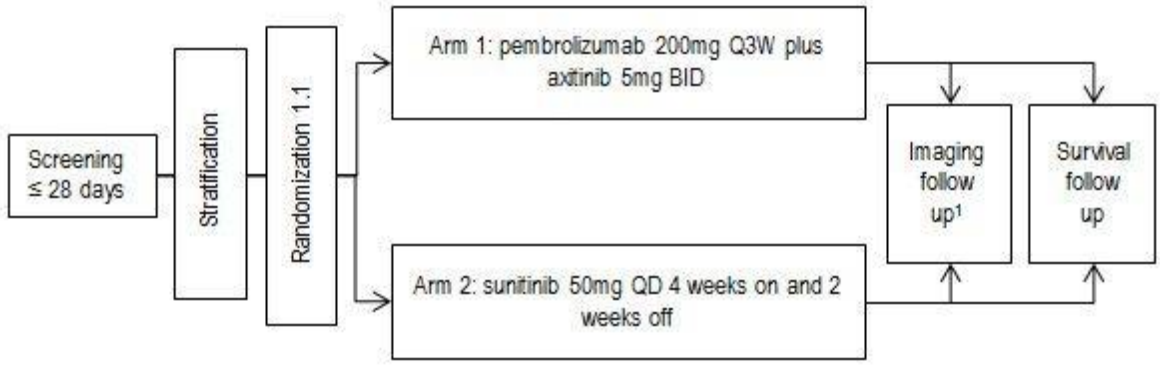
This trial will use a group-sequential design that includes 3 total analyses: 2 planned analyses for PFS (1 interim analysis and then final) and 3 planned analyses for OS (2 interim analyses and final). The first interim analysis (IA1) will be performed after enrollment has been completed, once a minimum follow up of 7 months and a minimum of 305 PFS events by BICR have been achieved. At IA1, approximately 48% of the final required OS events (~ 195 death events) are expected. The second interim analysis (IA2) will be performed when approximately 74% of the final required OS events (or 299 death events) have accrued. At IA2, final PFS analysis will also be performed if statistical significance of PFS has not yet achieved at IA1. The final OS analysis will be performed after a total of 404 death events have accrued. The study will conclude after the clinical cutoff for the final OS analysis has been achieved. Study assumptions, sample size calculations, and details and timing of interim and final analyses are described in detail in Section 8.0 – Statistical Analysis Plan (SAP).

The study will have an external Data Monitoring Committee (eDMC) to monitor safety during the course of the study, to evaluate efficacy and safety data at the interim analyses, and to provide recommendations for the study in accordance with the eDMC charter and the SAP.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



[1]Subjects who discontinue study treatment for reasons other than BICR-verified PD should continue with imaging assessments per the protocol defined schedule until PD is BICR verified or further confirmed by investigator, initiation of a new anti-cancer treatment, death, withdrawal of consent or study conclusion or early termination, whichever occurs first.

Figure 1 Study Schema

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male/female adult subjects (≥18 years of age) with mRCC.

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate and compare PFS per RECIST 1.1 as assessed by BICR in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.

Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to PFS as assessed by BICR per RECIST 1.1.

(2) **Objective:** To evaluate and compare OS in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.

Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to OS.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:** To compare ORR and DCR per RECIST 1.1 as assessed by BICR in subjects treated with a combination of pembrolizumab plus axitinib versus sunitinib monotherapy. DOR will also be evaluated.

Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to ORR as assessed by BICR per RECIST 1.1.

(2) **Objective:** To evaluate PFS rate per RECIST 1.1 as assessed by BICR at 12, 18, and 24 months based on data adequacy; to evaluate OS rates at 12, 18, and 24 months based on data adequacy.

(3) **Objective**: To evaluate and compare safety and tolerability profiles in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.

(4) **Objective**: To compare time to deterioration (TTD) based on the Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms (FKSI-DRS) scale in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.

(5) **Objective:** To assess the longitudinal score changes from baseline to 42 weeks as measured by European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 global health status/quality of life scale.

3.3 Exploratory Objectives

(1) **Objective:** To evaluate PFS, ORR, DOR, and DCR per immune-related RECIST (irRECIST) as assessed by BICR in subjects treated with pembrolizumab plus axitinib or sunitinib monotherapy.

(2) **Objective**: To characterize utility in subjects using the European Quality of Life (EuroQol) EQ-5D-3L.

(3) **Objective:** To characterize the pharmacokinetics (PK) of pembrolizumab in subjects treated with pembrolizumab plus axitinib.

(4) **Objective:** To identify molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to pembrolizumab/axitinib treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of the pembrolizumab/axitinib combination.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab (MK-3475). Refer to the approved labeling for detailed background information on axitinib and sunitinib.

4.1.1 Disease Background: Advanced Renal Cell Carcinoma

4.1.1.1 Epidemiology and Disease Characteristics of RCC

Renal cell carcinoma accounts for 2% to 3% of all adult malignancies, representing the seventh most common cancer in men and the ninth most common cancer in women. Worldwide, there are an estimated 209,000 newly diagnosed cases of RCC and an estimated 102,000 deaths per year [4]. In the United States (US), the expected number of new cases and deaths from kidney and renal pelvis cancer in 2016 is 62,700 and 14,240, respectively [5]. Approximately 90% of renal tumors are RCC and approximately 80% of these are of clear cell histology. Other less common cell types include papillary, chromophobe,

translocation, and collecting duct tumors [6]. Smoking and obesity are established risk factors for RCC. Several hereditary conditions, such as von Hippel-Lindau disease, predispose patients to having an increased risk of developing RCC [6].

At the initial diagnosis, approximately 65% of patients have localized disease; 16% have regional spread, and 16% have distant metastasis [5]. Recent epidemiologic data from the US indicates that the 5-year survival rate has improved over time. However, the 5-year survival rate for patients with distant metastasis is still considerably lower than that of localized disease (approximately 12% versus 92% respectively) [5]. The most important prognostic factors for survival include tumor stage, grade, degree of local extent, presence of regional nodal disease, and distant metastasis [6].

4.1.1.2 Current Treatment Options for Advanced RCC

Advanced RCC has previously been treated with immunotherapies such as interferon alpha (IFNα) and interleukin 2 (IL-2) with overall limited clinical activity. High-dose IL-2, however, had demonstrated durable responses in a small number of highly selected patients in Phase II non-randomized trials. As a result, it received Food and Drug Administration (FDA) approval in 1976 for treating advanced RCC in selected patients [7].

Since 2005, a number of novel anti-cancer agents have been developed, which have demonstrated significant improvement in clinical efficacy, with acceptable safety profiles in patients with advanced RCC in large randomized Phase III trials. These agents include the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, sorafenib, and axitinib, the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (given in combination with IFNα), and the mammalian target of rapamycin (mTOR) inhibitors, temsirolimus, and everolimus.

Table 1 summarizes the clinical efficacy of systemic treatments in patients with treatment-naïve advanced RCC from randomized Phase III studies. Based on the results of the sunitinib versus IFNα trial, the pazopanib versus placebo trial, and the bevacizumab plus IFNα versus IFNα trial, sunitinib, pazopanib, and bevacizumab plus IFNα received approval from the FDA and European Medicines Agency (EMA) for the treatment of advanced RCC. Pazopanib has also demonstrated non-inferiority to sunitinib for PFS and with similar OS in a large randomized Phase III study using a non-inferiority design. Temsirolimus received regulatory approval as a first-line treatment for poor-risk patients with advanced RCC.

Table 1 Summary of Clinical Efficacy from Randomized Phase III Studies in First-line Advanced RCC

Study (N)	Median PFS (months)	Median OS (months)	ORR (%)	Reference
Sunitinib vs. IFNα (N = 750)	11.0 vs. 5[a]	26.4 vs. 21.8	31 vs. 6[a]	Motzer et al. NEJM 2007 [8] Motzer et al. JCO 2009 [9]
Pazopanib vs. Placebo (N = 233)	11.1 vs. 2.8[a]	22.9 vs. 20.5	30 vs. 3[a]	Sternberg et al. JCO 2010 [10] Sternberg et al. EJC 2013 [11]
Bevacizumab + IFNα vs. IFNα (N = 649)	10.2 vs. 5.4[a]	23.2 vs. 21.3	31 vs. 13[a]	Escudier et al. Lancet. 2007 [12] Escudier et al. JCO 2010 [13]
Sunitinib vs. pazopanib (N = 1110)[b]	9.5 vs. 8.4	29.3 vs. 28.4	24 vs. 31	Motzer et al. NEJM 2013 [14]
Axitinib vs. sorafenib (N = 288; 2:1 randomization)	10.1 vs. 6.5	Not reported	32 vs. 15[a]	Hutson et al. Lancet. 2013 [15]
Temsirolimus vs. IFNα (N = 416)[c]	5.5 vs. 3.1[a]	10.9 vs. 7.3[a]	8.6 vs. 4.8	Hudes et al. NEJM 2007 [16]

Abbreviations: EJC = *European Journal of Cancer;* IFNα = interferon alpha; JCO = *Journal of Clinical Oncology;* NEJM = *New England Journal of Medicine;* ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma.

a. Results demonstrated statistically significant improvement of the testing arm versus the control arm.
b. The sunitinib versus pazopanib study used a non-inferiority design which demonstrated that pazopanib was noninferior to sunitinib with the primary endpoint PFS meeting the predefined non-inferiority margin
c. OS was the primary endpoint for this study while other trials used PFS as the primary endpoint. This study enrolled a poor-risk population while other trials enrolled a majority of subjects with good or intermediate risks.

Based on the data described above, the current recommendations by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) for first-line treatment of advanced RCC include sunitinib, pazopanib, and bevacizumab plus IFNα. Temsirolimus is recommended as a first-line treatment for patients with poor prognosis. High-dose IL-2 and sorafenib are recommended for selected patients. In addition, NCCN also included axitinib as a treatment choice based on data from a Phase III randomized study of axitinib versus sorafenib in treatment-naïve patients in whom the primary endpoint PFS showed no difference between the 2 arms (10.1 months for axitinib versus 6.5 months for sorafenib (hazard ratio [HR] = 0.77; 95% confidence interval [CI]: 0.56 to 1.05; not statistically significant). However, the ORR for axitinib was significantly higher than that for sorafenib (32% versus 15%; one-sided P = 0.0006) [15].

Three TKIs have been evaluated as second- or third-line treatment for patients with advanced RCC:

Sorafenib was approved by the FDA for advanced RCC based on a Phase III randomized trial demonstrating improvement in PFS compared to placebo in patients having failed prior cytokine treatments. The efficacy results for sorafenib compared to placebo were: median PFS 167 versus 84 days; HR: 0.44; P<0.00001; response rate (RR): 2% versus 0%; median OS: 17.8 versus 15.2 months, HR: 0.88; P = 0.146 [17].

Everolimus was approved by the FDA and EMA for the treatment of advanced RCC after failure of prior VEGF-targeted therapy based on a Phase III randomized trial demonstrating statistically significant improvement in PFS (median 4.9 months for everolimus versus

1.9 months for placebo; HR: 0.33 [0.25 to 0.43]; P<0.0001) but no OS benefit (median 14.8 months for everolimus versus 14.4 months for placebo; HR: 0.87; P= 0.162) [18]. The ORR was 2% for everolimus and 0% for placebo [19].

Axitinib was evaluated in a phase III randomized study compared to sorafenib in advanced/metastatic RCC patients after failure of one prior anti-angiogenic agent. The primary endpoint of PFS was significantly improved in axitinib vs. sorafenib (median PFS 6.7 vs. 4.7 respectively; HR: 0.665, 95% CI, 0.544 to 0.812, P < 0.0001). The secondary endpoint of ORR was also significantly higher in axitinib vs. sorafenib (19% vs. 9% respectively, P = 0.0001). However, the final OS data showed no significant difference between the two arms; median OS was 20.1 months for axitinib vs. 19.2 months for sorafenib (HR: 0.969, 95% CI, 0.800 to 1.174, one-sided P = 0.3744). Based on these data, axitinib gained approval for use in advanced RCC patients after failure of one prior systemic treatment (FDA) [22] or after failure of sunitinib or cytokine therapy (EMA).

Subsequent treatments following the failure of first-line therapy have been divided into 2 categories: 1) treatment choices after prior cytokine therapy and 2) treatment choices after prior targeted therapy. Axitinib, sorafenib, sunitinib, and pazopanib have demonstrated improved efficacy (PFS) in a cytokine failure population and hence, have been recommended by the NCCN and ESMO for use in this population. However, cytokine use in the first-line setting has been diminishing in favor of the approved anti-angiogenic agents. The following treatments are recommended by NCCN and ESMO after prior targeted therapy: axitinib, everolimus, sorafenib, sunitinib, pazopanib, bevacizumab plus IFNα, temsirolimus and nivolumab.

Recently, nivolumab and cabozantinib have received approval by the FDA to treat patients with advanced RCC who have received prior anti-angiogenic therapy.

Nivolumab is an immune checkpoint inhibitor targeting programmed cell death protein 1 (PD-1). The approval was based on data from a randomized Phase III open-label study in patients with advanced RCC following prior treatment with targeted therapy. Nivolumab demonstrated statistically significant improvement in the primary endpoint of OS versus everolimus during the planned interim analysis (median 25.0 months versus 21.8 months; HR: 0.73 (98.5% CI: 0.57 to 0.93; P=.002 met the pre-specified significance P≤.0148). The ORR was 25% for nivolumab versus 5% for everolimus (odds ratio 5.98; 95% CI: 3.68 to 9.72; P<.001). PFS was not significantly improved with a median PFS 4.6 months for nivolumab versus 4.4 months for everolimus (HR: 0.88; 95% CI: 0.75 to 1.03; P=.11) [24].

Cabozantinib is a multi-target TKI targeting VEGFR, MET, and AXL. In a randomized Phase III trial versus everolimus in patients who failed prior to targeted therapy, cabozantinib demonstrated significant improvement in the primary endpoint PFS (median 7.4 months versus 3.8 months; HR: 0.58; 95% CI: 0.45 to 0.75; P<.001) and secondary endpoint ORR (21% versus 5%; P<.001). The final OS was significantly improved compared to everolimus (median 21.4 vs. 16.5 months; HR: 0.66; 95% CI: 0.53 to 0.83; P=.0003) [25, 26].

4.1.1.3 Targeting PD-1 Immune Checkpoints for Cancer Treatments

The adaptive immune system plays a major role in controlling and eradicating cancer via a process called cancer immunosurveillance. Cytotoxic T lymphocytes cells (CTLs, also called CD8+ or effector T-cells), which are central to responses within the adaptive immunity, can be activated and execute cell killing function upon recognizing tumor-specific or tumor-associated antigens presented by antigen presenting cells (APCs) [27, 28, 29].

T-cell activation is tightly controlled by co-stimulatory and co-inhibitory signals which are triggered by the interactions between T-cell receptors (TCRs) and their ligands. The inhibitory pathways, also called immune checkpoints, are crucial for maintaining self-tolerance and minimizing collateral tissue damage in the event of immune response to pathogens. Programmed cell death protein 1 (PD-1) is a member of the extended CD28/CTLA4 family of T-cell regulators and PD-1-mediated immune checkpoint plays a key role in controlling effector T-cell activities within peripheral tissues, including tumors. Binding of PD-1 to its ligands programmed death-ligand 1 (PD-L1) and/or programmed death-ligand 2 (PD-L2) will trigger downstream signaling inside T-cells leading to decreased production of cytokines such as IL-2 and interferon γ, inhibition of cell proliferation, reduced T-cell effect or function and survival [27, 30, 31, 32]. PD-L1 was found expressed on the surface of many human cancer cells including RCC; and PD-L1 expression by tumor cells was found associated with poor prognosis in several cancers including RCC [33].

Human cancer can exploit immune checkpoint pathways to escape immunosurveillance. Restoration of endogenous anti-cancer immunity by immune checkpoint blockade has thus become an attractive strategy of cancer immunotherapy. The success in the clinical development of immune checkpoint inhibitors has significantly changed the landscape of cancer treatment [28, 29, 30, 34, 35, 36, 37].

4.1.2 Pharmaceutical and Therapeutic Background

4.1.2.1 Anti-PD-1 Antibody Pembrolizumab

Pembrolizumab is a highly selective and potent humanized monoclonal antibody of the IgG4/kappa isotype which is designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. As of September 2015, the safety and clinical activity of pembrolizumab have been evaluated in over 12,000 patients across multiple tumor types via clinical trials and the Melanoma Expanded Access Program. Pembrolizumab was generally well tolerated. As of December 2015, pembrolizumab monotherapy has received full approval from the FDA and EMA for the treatment of patients with unresectable or metastatic melanoma, and it has received accelerated approval for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. The recommended dose for these 2 indications is 2 mg/kg Q3W [38].

4.1.2.2 Summary of Pembrolizumab Clinical Efficacy and Safety

Refer to the pembrolizumab IB/approved labeling for details regarding pembrolizumab preclinical and clinical pharmacology studies as well as clinical safety.

Pembrolizumab clinical activity in advanced melanoma

In study KEYNOTE-001 (KN001), the Phase I first-time-in-human study, pembrolizumab was evaluated in a cohort of 135 subjects with advanced melanoma who were either treatment-naïve (31%) or had progressed from prior ipilimumab (69%), at a dosage of 2 mg/kg Q3W, 10 mg/kg every 2 weeks (Q2W), or 10 mg/kg Q3W. The study showed an ORR of 38% (95% CI: 25% to 44%) in the overall population. Response was durable in the majority of subjects; median DOR was not reached with median follow up of 11 months [39]. In an expansion cohort, 173 subjects with advanced melanoma who had progressed from prior ipilimumab were randomly assigned to receive pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W. Similar efficacy results were observed in the 2 arms: ORR was 26% in each arm; DCR was 51% and 50%, respectively. With a median follow up of 8 months, 88% of responders were still ongoing at the clinical cutoff. Even though most responses were observed at the first scan, initial response could occur as late as 11 months and CR could occur as late as 16 months [40].

Clinical efficacy of pembrolizumab in advanced melanoma was further demonstrated in 2 large randomized trials. In study KEYNOTE-002 (KN002) (N = 540), the efficacy and safety of pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W were compared with chemotherapy in subjects refractory to ipilimumab. The 6-month PFS rates were significantly improved in the 2 pembrolizumab arms compared with the chemotherapy arms. The ORR per independent review was 21% in the pembrolizumab 2 mg/kg Q3W arm and 25% in the 10 mg/kg Q3W arm compared to 4% in the chemotherapy arm ($P<0.0001$ for both comparisons). At the time of analysis, median DOR in the pembrolizumab arms was not reached; responses were ongoing in 92% and 87% of responders in the 2 pembrolizumab arms, respectively, versus 63% in the chemotherapy arm. There was no statistically significant difference in efficacy parameters between the 2 pembrolizumab arms [41].

In the Phase III Study KEYNOTE-006 (KN006) (N = 834, unresectable advanced melanoma population), subjects were randomized in a 1:1:1 ratio to receive pembrolizumab at 10 mg/kg Q2W, 10 mg/kg Q3W, or ipilimumab at 3 mg/kg Q3W. Subjects who received pembrolizumab (10 mg/kg Q2W or 10 mg/kg Q3W) showed statistically significant and clinically meaningful improvement compared to those who received ipilimumab in the estimated 6-month PFS rate (47.3%, 46.4% and 26.5%, respectively), one-year OS rate (74.1%, 68.4%, and 58.2%, respectively), and ORR (33.7%, 32.9%, and 11.9%, respectively). At the time of analysis, median OS was not reached in any treatment group. Responses were ongoing in 89.4% and 96.7% of the Q2W and Q3W pembrolizumab-treated groups, respectively, and in 87.9% of ipilimumab-treated patients after a median follow up of 7.9 months [42].

Pembrolizumab clinical activity in advanced NSCLC

In study KN001, clinical efficacy and safety were evaluated in 495 subjects with NSCLC after receiving pembrolizumab treatment at 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W. The study also evaluated the association between PD-L1 expression in tumor tissue

samples and the clinical efficacy by assigning 182 subjects to the training set and 313 subjects to the validation set. In the overall population (N = 495), ORR was 19.4% (95% CI: 16.0 to 23.2) and median DOR was 12.5 months. In the validation data set, ORR was 45.2% (95% CI: 33.5 to 57.3) in subjects with ≥ 50% of tumor cells positive for PD-L1 expression (n = 73); ORR was 16.5% (95% CI: 9.9 to 25.1) in patients with 1% to 49% tumor cells positive (n = 103) and 10.7% (95% CI: 2.3 to 28.2) in patients with <1% tumor cells positive (n = 28) for PD-L1 expression. These data indicate a potential for PD-L1 to be used as a patient enrichment biomarker for better clinical efficacy [43].

Pembrolizumab clinical activity in other advanced cancers

Study KEYNOTE-012 (KN012) is an ongoing non-randomized, multi-cohort, Phase Ib study to evaluate the safety and clinical activity of pembrolizumab 10 mg/kg Q2W in subjects with advanced solid tumors that have positive PD-L1 expression either in tumor cells or stroma cells. Most of these subjects were heavily pretreated. Subjects with advanced gastric cancer, head and neck cancer, urothelial tract cancer, and triple negative breast cancer were enrolled. An ORR of 31% was observed in subjects with advanced gastric cancers (N = 39) [44]; an ORR of 27.6% (95% CI: 12.7 to 47.2%) was observed in subjects with advanced urothelial tract cancer (N = 33) [45]; an ORR of 24.8% (95% CI: 17.3 to 33.6%) was observed in subjects with advanced head and neck cancer (N = 132) [46]. Impressive responses have also been reported by Nanda et al., in triple negative breast cancer at the 2014 San Antonio Breast Cancer Symposium [47]. In all these cohorts, durable responses were observed in those who responded including some durable stable diseases (SDs). Higher PD-L1 expression seemed to be associated with higher response.

4.1.2.3 Axitinib

Axitinib (INLYTA®, AG-013736) is an oral, small molecule, TKI selective for VEGFRs 1, 2 and 3 and is approved multinationally for the treatment of advanced RCC after failure of 1 prior systemic therapy (actual indication varies according to region/country).

Axitinib is an ATP-competitive inhibitor that binds to the unphosphorylated (non-activated) "DFG-out" conformation of the catalytic domain of a receptor tyrosine kinase. In enzymatic assays, axitinib was found to be highly potent (K_i = 28 picomolar) against the kinase activity of juxta-membrane domain containing human VEGFR 2 recombinant protein. In additional kinase assays, axitinib showed potent and ATP-competitive inhibition of the VEGFRs 1, 2, 3 and PDGFR-β, but not other closely-related family kinases. Receptor binding studies and cell-based assays, confirmed that axitinib is a potent and selective inhibitor of VEGFRs 1, 2 and 3. Axitinib was shown to have antiangiogenic activity in a number of models, including a spontaneous pancreatic islet-cell tumor of RIP-TAG-2 transgenic mice model, and demonstrated anti-tumor efficacy including marked cyto-reductive anti-tumor activity in multiple tumor models implanted in athymic mice.

4.1.2.4 Summary of Clinical Efficacy and Safety of Axitinib in Advanced RCC

Axitinib monotherapy has been evaluated in advanced RCC in 2 randomized Phase III trials. The Phase III study of axitinib versus sorafenib in advanced RCC patients who failed prior systemic treatments demonstrated a statistically significant advantage for axitinib over sorafenib for the primary PFS endpoint (median PFS 6.7 months versus 4.7 months; HR:

0.67; 95% CI: 0.54 to 0.81; P<.0001) but not OS (median 20.1 months for axitinib vs. 19.2 months for sorafenib; HR: 0.969; 95% CI: 0.800 to 1.174; one-sided P=.3744) and has been approved by the FDA and EMA for treating advanced RCC after failure of prior treatment [20, 21]. The most common (≥20%) adverse reactions observed in this study following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, decreased weight, vomiting, asthenia, and constipation [20].

The Phase III study of axitinib vs. sorafenib in treatment-naïve advanced clear cell RCC had a 2:1 randomization (axitinib N=192, sorafenib N=96). There was no significant difference in median PFS between subjects treated with axitinib or sorafenib; 10.1 months (95% CI 7.2, 12.1) vs. 6.5 months (95% CI 4.7, 8.3), respectively, with stratified hazard ratio 0.77, (95% CI 0.56, 1.05). The ORR in the axitinib arm (32%) was statistically significant compared to the sorafenib arm (15%) as assessed by an Independent Review Committee, with a risk ratio of 2.21, (95% CI 1.31, 3.75, stratified one sided P=0.0006) [15]. Based on this data, axitinib was recommended by NCCN as a first-line treatment choice for advanced RCC [6]. The most common AEs (≥20%) observed with axitinib were diarrhea, hypertension, weight decrease, fatigue, decreased appetite, hand-foot syndrome, dysphonia, asthenia, hypothyroidism and nausea [15].

Overall, the AEs reported for axitinib in clinical studies were considered manageable and generally reversible. Further details on clinical pharmacology and safety can be found in the axitinib label [22, 23].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

In this study, we will evaluate a novel drug combination including an effective anti-angiogenic agent axitinib and a PD-1 immune checkpoint inhibitor pembrolizumab in as a first-line treatment for advanced RCC. The rationale is as follows:

1. **Advanced RCC remains an area with unmet medical need.** Even though VEGF/VEGFR targeting anti-angiogenic agents, such as sunitinib, pazopanib, axitinib, and bevacizumab plus IFNα, have collectively made substantial improvement in the outcome of advanced RCC patients, most patients will progress within 2 years following a standard first-line treatment. As of now, the best median OS seen with first-line advanced RCC treatments in a population with good and intermediate prognosis was approximately 28 to 29 months as shown in the Phase III sunitinib versus pazopanib trial [14]. In a meta-analysis by Heng et al. [2] on 645 patients who received first-line anti-VEGF/VEGFR agents including sunitinib, sorafenib, and bevacizumab within the US and Canada, the median survival was 22 months. Based on Surveillance, Epidemiology, and End Results (SEER) data from 2004-2010, the 5-year survival rate of advanced RCC was only 12% [5]. Therefore, further development of novel agents with durable clinical benefit and curative effects is still highly needed for advanced RCC.

2. **Axitinib, a potent VEGFR TKI, has established single agent clinical efficacy in advanced RCC.** Even though the Phase III randomized study of axitinib versus sorafenib in the first-line setting did not demonstrate statistically significant improvement in the primary endpoint of PFS for axitinib compared to sorafenib, the efficacy results of axitinib (PFS of 10.1 months and ORR of 32%) were comparable to that of other standard-of-care first-line agents (see Table 1). Therefore, axitinib has been listed as a choice of treatment by NCCN for treatment-naïve advanced RCC patients. Axitinib is an approved agent for advanced RCC patients who have failed a prior therapy [6].
3. **RCC has long been considered an immune-reactive tumor** based on anecdotal reports of spontaneous remissions in advanced RCC patients with evidence of antigen-specific lymphocyte infiltration of tumor tissues [48] and the fact that high-dose IL-2 could produce durable long-term response in a small subset of advanced RCC patients. In RCC, upregulation of PD-1 receptor on tumor-infiltrating lymphocytes and its ligand PD-L1 on tumors is associated with more aggressive disease and poor prognosis [32, 49]. The evidence above supports targeting RCC with an immunotherapeutic approach. Even though pembrolizumab monotherapy has not been evaluated in advanced RCC, single agent anti-tumor activity has been demonstrated by another anti-PD-1 antibody, nivolumab, in advanced RCC. In a Phase I study that included 33 heavily pretreated advanced RCC patients, ORR was achieved in 9/33 (27%) of patients with another 9 patients (27%) achieving stable disease at the 24-week follow-up. Five patients had durable responses longer than 1 year [50].
4. **Preliminary results from a Phase 1b study of pembrolizumab in combination with axitinib has shown promising efficacy results and an acceptable safety profile.** Study KN035 (A4061079) is a Phase Ib study evaluating safety, PK and pharmacodynamics of axitinib in combination with pembrolizumab in treatment-naïve advanced RCC patients. The study enrolled a total number of 52 subjects. Eleven subjects were enrolled in the initial dose finding phase in which axitinib 5 mg BID (administered orally) plus pembrolizumab 2 mg/kg Q3W (administered intravenously) were evaluated as the target dose level. Of these 11 subjects, the median age was 63 years, 8 were male and 9 had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Three dose-limiting toxicities (DLTs) were reported: transient ischemic attack in 1 subject and reduction in the dose of axitinib to <75% the target dose level in 2 subjects because of treatment-related toxicity. Axitinib 5 mg BID plus pembrolizumab 2 mg/kg Q3W were identified as the recommended doses for the expansion phase.

Following the dose finding stage, an additional 41 treatment-naïve advanced RCC patients were enrolled (last subject enrolled in September 2015). The safety of the entire study population (N = 52) is summarized here based on a data cutoff of March 2016 (data not published). The demographic features are typical for that of an advanced RCC population: median age was 63 years, 78.8% male and 86.5% white. All had an ECOG performance status of 0 and 1. Of the 52 patients, 12 had discontinued pembrolizumab treatment: 7 (13.5%) due to AE, 4 (7.7%) due to PD, and 1 (1.9%) for other reasons; 14 had discontinued axitinib treatment: 8 (15.4%) due to AEs, 4 (7.7%) due to PD, 1 (1.9%) of each

due to patient refusal and other reasons. The median days on treatment by cutoff date was 211 days. The incidences of AEs due to all causalities were: all-grade, 100%; Grade 4, 3.8%; Grade 3, 53.8%; Grade 2, 32.7% and Grade 1, 9.6%. There were no Grade 5 AEs. All-grade AEs ≥ 20% are displayed in Table 2. Most laboratory abnormalities were Grade 1 or 2 (Table 3).

Table 2 Summary of Treatment-emergent AEs ≥ 20% (n, %) of All Causality

AE terms	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Any AEs	52 (100)	5 (9.6)	17 (32.7)	28 (53.8)	2 (3.8)
Diarrhea	37 (71.2)	26 (50.0)	8 (15.4)	3 (5.8)	0
Fatigue	37 (71.2)	19 (36.5)	16 (30.8)	2 (3.8)	0
Dysphonia	22 (42.3)	20 (38.5)	2 (3.8)	0	0
Hypertension	19 (36.5)	2 (3.8)	7 (13.5)	10 (19.2)	0
Hypothyroidism	19 (36.5)	8 (15.4)	11 (21.2)	0	0
ALT increased	18 (34.6)	8 (15.4)	7 (13.5)	3 (5.8)	0
Decreased appetite	18 (34.6)	13 (25.0)	4 (7.7)	1 (1.9)	0
Hand-foot syndrome	18 (34.6)	5 (9.6)	12 (23.1)	1 (1.9)	0
Cough	17 (32.7)	16 (30.8)	1 (1.9)	0	0
Nausea	17 (32.7)	12 (23.1)	4 (7.7)	1 (1.9)	0
AST increased	16 (30.8)	8 (15.4)	5 (9.6)	3 (5.8)	0
Arthralgia	14 (26.9)	9 (17.3)	5 (9.6)	0	0
Dizziness	12 (23.1)	11 (21.2)	0	1 (1.9)	0
Dyspnea	12 (23.1)	7 (13.5)	3 (5.8)	1 (1.9)	1 (1.9)
Headache	12 (23.1)	5 (9.6)	4 (7.7)	3 (5.8)	0
Oral pain	11 (21.2)	9 (17.3)	1 (1.9)	1 (1.9)	0
Proteinuria	11 (21.2)	5 (9.6)	6 (11.5)	0	0
Weight decreased	11 (21.2)	7 (13.5)	2 (3.8)	3.8	0

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Percentage is based on the number of patients receiving at least 1 dose of study treatment.

Table 3 Laboratory Results (n, %) by Maximum CTCAE Grade (N = 52)

Lab parameters	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Hematology					
Anemia	25 (48.1)	25 (48.1)	0	0	0
Hemoglobin increased	9 (17.3)	6 (11.5)	1 (1.9)	2 (3.8)	0
Lymphocyte count increased	3 (5.8)	0	1 (1.9)	2 (3.8)	0
Lymphopenia	25 (48.1)	8 (15.4)	13 (25.0)	4 (7.7)	0
Neutrophils count decreased	4 (7.7)	3 (5.8)	1 (1.9)	0	0
Platelets count decreased	13 (25.0)	11 (21.2)	2 (3.8)	0	0
White Blood Cells count decreased	6 (11.5)	5 (9.6)	1 (1.9)	0	0
Chemistry					
ALT increased	27 (51.9)	19 (36.5)	6 (11.5)	2 (3.8)	0
Alkaline Phosphatase increased	16 (30.8)	16 (30.8)	0	0	0
AST increased	27 (51.9)	22 (42.3)	5 (9.6)	0	0
Bilirubin (Total) increased	10 (19.2)	5 (9.6)	2 (3.8)	3 (5.8)	0
Creatinine increased	45 (86.5)	38 (73.1)	5 (9.6)	0	2 (3.8)
Hypercalcemia	12 (23.1)	11 (21.2)	0	0	1 (1.9)
Hyperglycemia	45 (86.5)	30 (57.7)	14 (26.9)	1 (1.9)	0
Hyperkalemia	14 (26.9)	8 (15.4)	4 (7.7)	1 (1.9)	1 (1.9)
Hypermagnesemia	5 (9.6)	3 (5.8)	0	2 (3.8)	0
Hypernatremia	0	0	0	0	0
Hypoalbuminemia	12 (23.1)	12 (23.1)	0	0	0
Hypocalcemia	7 (13.5)	5 (9.6)	2 (3.8)	0	0
Hypoglycemia	6 (11.5)	5 (9.6)	1 (1.9)	0	0
Hypokalemia	8 (15.4)	7 (13.5)	0	1 (1.9)	0
Hypomagnesemia	4 (7.7)	3 (5.8)	1 (1.9)	0	0
Hyponatremia	23 (44.2)	19 (36.5)	0	4 (7.7)	0
Hypophosphatemia	12 (23.1)	1 (2.0)	8 (16.0)	3 (6.0)	0

Preliminary unpublished efficacy data from these 52 patients showed an ORR of 67.3% (CR = 3.8%, PR = 63.5%); SD of 21.2%; PD of 3.8%, and 4 subjects (7.7%) with best response indeterminate.

Based on the scientific rationale of targeting angiogenesis and immune-check point pathways, as well as the promising data from these 52 patients, further evaluation of the combination regimen of axitinib plus pembrolizumab is warranted. We expect that this novel combination may provide additional clinical benefit in advanced RCC compared to the current standard of care in the first-line setting.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Dose Selection / Regimen for the Experimental Arm

The following dose regimen is selected for the axitinib/pembrolizumab combination:

- Axitinib 5 mg BID dosed continuously
- Pembrolizumab 200 mg Q3W

In the Phase Ib study KN035 (A4061079) that evaluated the combination of axitinib and pembrolizumab, axitinib 5 mg BID continuous dosing and pembrolizumab 2 mg/kg Q3W was determined as the recommended combination regimen (see Section 4.2.1). However, based on collective evidence, a flat dose of 200 mg Q3W has been determined for pembrolizumab used either as monotherapy or in combination regimens.

Rationale for using 200 mg Q3W dose for pembrolizumab

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the US and several other countries for treatment of melanoma is 2 mg/kg Q3W. Information on the rationale for selecting a 200 mg Q3W dose is summarized below.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma and NSCLC in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with the 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap with those obtained from the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma and NSCLC as associated with maximal clinical response.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma and NSCLC can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific

tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and will reduce the potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest that 200 mg Q3W is the appropriate dose for pembrolizumab.

4.2.2.2 Rationale for the Choice of Comparator

This study will evaluate the efficacy and safety of a novel combination of a VEGFR TKI axitinib and a PD-1 immune checkpoint inhibitor pembrolizumab in treatment-naïve advanced RCC. The NCCN and ESMO recommended standard treatment in this setting includes sunitinib, pazopanib, bevacizumab plus IFNα based on highly significant results from large Phase III randomized trials. Sunitinib is the most frequently used first-line treatment in advanced RCC and has a well characterized safety profile therefore sunitinib is selected as a control for the study.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

This is a pivotal Phase III randomized open-label study to evaluate the efficacy and safety of the combination of pembrolizumab plus axitinib compared with sunitinib monotherapy. The study includes dual primary efficacy endpoints: 1) PFS per RECIST 1.1 as assessed by BICR and 2) overall survival.

Progression-free survival has been used as an acceptable primary endpoint in randomized Phase III trials to support regulatory approval for new treatments in advanced RCC in both the first-line setting and in subjects who have failed prior treatments. In the first-line setting, all current approvals including sunitinib, pazopanib, and bevacizumab plus IFNα, but not temsirolimus, were based on demonstrating a statistically significant and clinically meaningful improvement in PFS without demonstrating survival benefit. Temsirolimus was approved only for the poor risk group based on demonstrating survival benefit in this subset of patients. Agents approved for subsequent treatments in advanced RCC were also based on PFS, including axitinib, sorafenib, and everolimus. Therefore, PFS is included as a primary endpoint for the study.

The primary analysis of PFS will be based on BICR in order to limit bias. Since this is an open-label study, measures have been taken to ensure that the central radiologist will be blinded to the treatment assignments of the subjects. In order to avoid PD being determined prematurely by the investigator, subjects with suspected radiologic progression first identified at the site will have all scans submitted for BICR verification of PD. The results of central PD verification will be communicated to the site promptly.

Overall survival is the ultimate gold standard endpoint to demonstrate superiority of anti-cancer therapy. Given the list of available therapies for advanced RCC for treatment beyond first-line and that the study allows subjects to select any subsequent anti-cancer treatment upon progression, the OS assessment is likely to be confounded by subsequent

treatments. The Sponsor will ensure that adequate information on subsequent therapies is collected and analyses are included to evaluate the confounding issues.

Secondary endpoints consist of ORR, DOR, and DCR per RECIST 1.1 as assessed by BICR. Durable response has been demonstrated with pembrolizumab and other immune checkpoint inhibitors in subsets of patients in multiple tumor types and provides meaningful supportive evidence for clinical efficacy.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and subjects may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of patients with melanoma enrolled in KEYNOTE-001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by irRECIST had longer OS than patients with progressive disease by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression.

irRECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al [51]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target lesions, and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and to make treatment decisions as well as by the BICR in support of the PFS, ORR, DOR, and DCR endpoints.

4.2.3.2 Safety Endpoints

The safety objective is to characterize the safety and tolerability of pembrolizumab in combination with axitinib in subjects with advanced mRCC as a first-line treatment. The following safety parameters will be analyzed: AEs and SAEs graded per NCI CTCAE, Version 4.0 criteria with time to onset/recovery, causality and outcome; changes in laboratory values, vital signs since baseline, treatment discontinuations and reason for discontinuation, death and cause of death, etc. Concomitant medications will be collected with time and reasons for use. These are routine safety parameters collected and analyzed in Phase II/III oncology trials.

4.2.3.3 Health-related Quality of Life Endpoints

FKSI-DRS, EORTC-QLQ-C30, and EuroQol EQ-5D-3L are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

The FKSI-DRS scale and global health status/quality of life scale from EORTC-QLQC30 are the key PRO endpoints. Although no formal hypothesis was formulated, the p-value on treatment comparisons will be provided. No multiplicity adjustment was performed.

The 9 items of the FKSI-DRS are summarized into a symptom scale ranging in score from zero (0) to thirty-six (36), with zero being the worst possible score and 36 being the best possible score [52]. The minimum important change in the FKSI-DRS used to define symptom progression is approximately a change of 2 points and that definition has been used for this mRCC symptom scale in other mRCC trials [19, 52, 53]. The Time-to-Deterioration of FKSI-DRS is defined as:

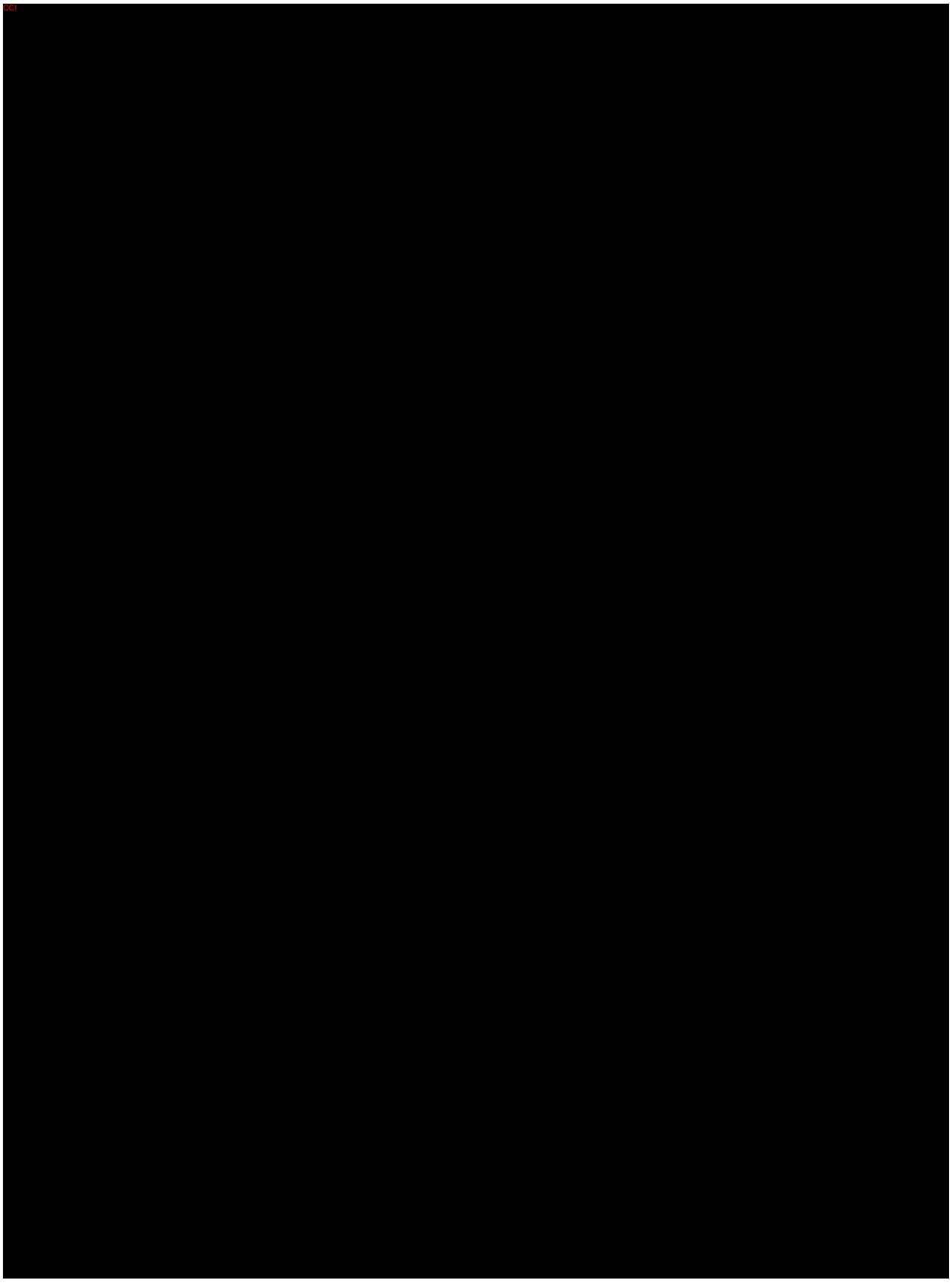
- The time to first onset of 2 or more decreases from baseline.
- The time to first onset of 2 or more decrease from baseline and confirmed by the second adjacent 2 or more decrease from baseline.
- The time to first onset of 2 or more decrease from previous nadir and confirmed by the second adjacent 2 or more decrease from nadir.

The longitudinal score changes of the EORTC QLQ-C30 global health status/quality of life scale (i.e., items 29 and 30) from baseline and the proportions of deterioration/stable/improvement at 42 weeks (i.e., based on expected median PFS of 11 months in the control group) into the study will be described. A 10-point decrease is often considered as the minimal clinical meaningful difference. Other supportive analyses include 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale.

EuroQol EQ-5D-3L is another set of endpoints as a measure of health outcome. The EuroQol EQ-5D-3L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life years (QALYs).

Electronic patient-reported outcomes (PROs), in the order of FKSI-DRS, EORTC QLQ-C30 and EuroQol EQ-5D-3L, will be completed by the patient prior to all other study procedures. See the Trial Flow Chart (Section 6.0) as well as Section 7.1.2.8 for details on PRO administration and timepoints.

4.2.3.4 Rationale for Planned Exploratory Biomarker Research



4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Pembrolizumab has received regulatory approval for multiple advanced cancer indications with more than 20,000 cancer participants having received pembrolizumab treatment in the clinical trial program as of 30-MAR-2017 [refer to pembrolizumab IB for up-to-date information]. Pembrolizumab has been established with a well-characterized safety profile. Pembrolizumab is well tolerated at doses up to 10 mg/kg Q2W and has demonstrated anti-cancer clinical activity and efficacy in a broad range of cancer indications (see Summary in Section 4.1.2.2). Axitinib is a VEGFR-TK inhibitor agent that has been approved for advanced RCC after a prior targeted therapy and has also been studied in treatment-naïve subjects with advanced RCC and shown acceptable efficacy (see Section 4.1.2.4). The combination of pembrolizumab 2 mg/kg Q3W and axitinib 5 mg BID continuous dosing has demonstrated promising preliminary efficacy with an ORR of 67% and a safety profile consistent with a combined safety profile from each agent based on data from 52 treatment-naïve advanced RCC patients (see Section 4.2.1 for further details). As the efficacy and safety profile of the pembrolizumab plus axitinib combination has not yet been characterized in a larger data set, participating subjects may experience side effects not yet observed or they may not respond to the combination. However, such risks exist with current standard of care treatments. At present, there are no curative systemic treatments for advanced or metastatic RCC and only approximately 30% of patients develop objective responses to the

current standard of care treatments (see summary in Section 4.1.1.2 and Table 1), all of which may cause severe side effects as described in the label for each drug.

Sunitinib has been approved by regulatory agencies globally for the treatment of advanced RCC and has been recommended as a choice of first-line treatment for advanced RCC by NCCN and ESMO guidelines (see Section 4.1.1.2).

Additional details regarding specific benefits and risks for subjects participating pembrolizumab clinical trial may be found in the accompanying IB and Informed Consent documents. Efficacy and safety risk information for using sunitinib and axitinib can also been found in the current label of each drug.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female adult (≥18 years) subjects with mRCC will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for future biomedical research. However, the subject may participate in the main trial without participating in future biomedical research.
2. Be ≥18 years of age on day of signing informed consent.
3. Have histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features.
4. Have locally advanced/metastatic disease, ie, newly diagnosed Stage IV RCC per American Joint Committee on Cancer or have recurrent disease.
5. Have measurable disease per RECIST 1.1 as assessed by the investigator /site radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Have received no prior systemic therapy for advanced RCC.
7. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion as required. Lesions cannot be previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides.

   Note: Tumor blocks are preferred over cut slides. Please refer to the Study Procedures Manual for important details regarding tumor tissue submission time window and process.
8. Have Karnofsky performance status (KPS) ≥ 70% as assessed within 10 days prior to randomization (see Section 12.4 for KPS description).

9. Subjects receiving bone resorptive therapy (including but not limited to bisphosphonate or RANK-L inhibitor) must have therapy initiated at least 2 weeks prior to randomization.
10. Demonstrate adequate organ function as defined in Table 4 and all screening laboratory tests should be performed within 10 days prior to randomization.

Table 4 Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mm^3 or ≥ 1.5 × 10^9 / L
Platelets	≥100,000 / mm^3 or ≥ 100 ×10^9 / L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L– without a red blood cell transfusion within 2 weeks of the screening test
Renal	
Serum creatinine **OR** calculated creatinine clearance (CrCl)[a] Note: GFR can also be used in place of creatinine or CrCl	≤1.5 × upper limit of normal (ULN) **OR** ≥40 mL/min for subjects with creatinine levels > 1.5 ×institutional ULN
Urine protein	< 2+ by dipstick urinalysis If dipstick is ≥ 2+, then 24 hr urine protein must be < 2 g, or urine protein creatinine ratio (UPC) must be < 2
Hepatic	
Serum total bilirubin	≤ 1.5 × ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as INR or PT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate;.
[a] Creatinine clearance should be calculated per institutional standard.

11. Female subjects of childbearing/reproductive potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    Note, in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

12. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

13. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.
2. Has had major surgery within 4 weeks, received radiation therapy within 2 weeks prior to randomization, or has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to prior treatment.
3. Has had prior treatment with any anti-PD-1, or PD-L1, or PD-L2 agent or an antibody targeting any other immune-regulatory receptors or mechanisms. Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, and GITR.
4. Has received prior systemic anti-cancer therapy for RCC (e.g., VEGF/VEGFR, chemotherapy or mTOR-targeting agents).

   Note: Prior neoadjuvant/adjuvant therapy for RCC is acceptable if completed > 12 months prior to randomization.

5. Has a history of severe hypersensitivity reaction (e.g., generalized rash/erythema, hypotension, bronchospasm, angioedema, or anaphylaxis) to axitinib or sunitinib.
6. Has a diagnosis of immunodeficiency OR is receiving a systemic steroid therapy exceeding physiologic corticosteroid dose or any other form of immunosuppressive therapy within 7 days prior to randomization, except in the case of central nervous system (CNS) metastases (see exclusion 9).
7. Has an active autoimmune disease requiring systemic treatment within the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) OR with a documented history of clinically severe autoimmune disease.

Note: Subjects with vitiligo, Sjögren's syndrome, Type 1 diabetes, or resolved childhood asthma/atopy will not be excluded from the study. Subjects requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from the study. Subjects with hypothyroidism, or adrenal or pituitary insufficiency who are stable on hormone replacement will not be excluded from the study.

8. Has a known additional malignancy that has progressed or has required active treatment in the last 3 years.

   Note: Basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ such as breast cancer in situ are acceptable if they have undergone potentially curative therapy.

9. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to randomization.
10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has a known history of Human Immunodeficiency Virus (HIV) infection (HIV 1 and/or 2 antibodies).

    Note: HIV 1 and/or 2 antibodies testing is required when the investigator has reason to suspect the subject has HIV infection or is otherwise mandated per local guidance.

13. Has a known history of Hepatitis B (eg, Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (eg, HCV RNA [qualitative] is detected).

    Note: HCV RNA testing is not required in those countries where local standard of care uses only Hepatitis C antibody testing as evidence of status of Hepatitis C.

14. Has received a live virus vaccine within 30 days of randomization (See Section 5.5.3 for further detail).
15. Has a clinically significant gastrointestinal (GI) abnormality including:

    - Malabsorption, total gastric resection, or any other condition that might affect the absorption of orally taken medication
    - Active GI bleeding, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy
    - Intraluminal metastatic lesion with suspected bleeding, inflammatory bowel disease, ulcerative colitis or other GI condition associated with increased risk of perforation

16. Has QT interval corrected for heart rate (QTc) ≥ 480 msec.
17. Has a history of any of the following cardiovascular conditions within 12 months of randomization:
    - Myocardial infarction
    - Unstable angina pectoris
    - Cardiac angioplasty or stenting
    - Coronary/peripheral artery bypass graft
    - Class III or IV congestive heart failure per New York Heart Association
    - Cerebrovascular accident or transient ischemic attack
18. Has a history of deep vein thrombosis or pulmonary embolism within 6 months of screening.
19. Has poorly controlled hypertension defined as systolic blood pressure (SBP) ≥ 150 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg.

    Note: measurement of screening blood pressure (BP) reading is based on an average of 3 readings at least 2 minutes apart. Subjects with initial screening BP ≥150/90 mm Hg can be treated with anti-hypertensive medication to achieve a well-controlled status and are eligible with reassessed SBP/DBP of < 150/90 mm Hg.
20. Has evidence of inadequate wound healing.
21. Has active bleeding disorder or other history of significant bleeding episodes within 30 days of randomization.
22. Has hemoptysis within 6 weeks prior to randomization.
23. Has current use (within 7 days of randomization) or anticipated need for treatment with drugs or foods that are known strong cytochrome P450 (CYP3A4/5) inhibitors including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice.

    NOTE: The topical use of these medications, such as 2% ketoconazole cream, is allowed.
24. Has current use (within 7 days of randomization) or anticipated need for treatment with drugs that are known strong CYP3A4/5 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort; or drugs that are known with proarrhythmic potential (see Section 5.5.3 for list of drugs).
25. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

26. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
27. Has had a prior solid organ transplant.
28. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 5.

Table 5 Trial Treatments

Treatment	Regimen	Route of Administration	Duration of treatment	Use in Study
Pembrolizumab/Axitinib Combination Arm				
Pembrolizumab	200 mg every 3 weeks (Q3W)	IV infusion	Up to 35 doses (about 24 months) or until PD is BICR verified or further confirmed by the investigator[a]	Experimental
Axitinib	5 mg twice daily (BID)	Orally (PO)	Continued treatment until PD is BICR verified or further confirmed by the investigator	Experimental
Sunitinib Monotherapy Arm				
Sunitinib	50 mg daily (QD) 4 weeks on, 2 weeks off	PO	Continued treatment until PD is BICR verified or further confirmed by the investigator	Comparator (standard of care)

Abbreviations: BICR=blinded independent central review; BID=twice daily; IV=intravenous; PD=progressive disease; PO=per os/by mouth; Q3W=every 3 weeks.

[a] Subjects in the pembrolizumab+axitinib arm may receive a second course of treatment with additional 17 doses. Details are described in Section 5.8.2.

Trial Treatment should begin within 3 days of randomization.

All supplies indicated in Table 5 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

The rationale for selection of the doses for the pembrolizumab plus axitinib combination and the sunitinib monotherapy to be used in this trial is provided in Section 4.0, Background and Rationale. Details on the preparation and administration of pembrolizumab are in the Pharmacy Manual.

5.2.2 Dose Modification

Every effort should be made to administer study treatments per the planned dosing schedule. Dose modification guidelines for a particular study treatment are to be followed if AEs are assessed as associated or potentially associated with that study treatment.

5.2.2.1 Dose Modification and Toxicity Management Guidelines for Adverse Events Potentially Associated with Pembrolizumab Treatment

Dose modification and toxicity management for immune-related AEs (irAEs) associated with pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for irAEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose Modification and Toxicity Management for Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reactions are provided in Table 7.

Table 7 Pembrolizumab-Associated Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping the drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further treatment with pembrolizumab**	Subject may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further treatment with pembrolizumab.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for reasons other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should be placed back on pembrolizumab within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in subject's study record.

5.2.2.2 Dose Modification Guidelines for Adverse Events Potentially Associated with Axitinib Treatment

Dose modification guidelines for treatment-related AEs that are potentially associated with axitinib are provided in Table 8. If a subject has a dose reduction due to treatment-related toxicity and the AEs resolve, the axitinib dose can be re-escalated to the previous dose if the subject can tolerate it and the AE does not recur.

Table 8 Dose Modification Guidelines for Drug-related AEs Potentially Associated with Axitinib Treatment

Toxicity	NCI CTCAE grade	Axitinib
Hypertension See Section 5.6.2 for monitoring/ management of axitinib-related hypertension	SBP ≤150 mm Hg and / or DBP ≤100 mm Hg	Continue at the same dose level Antihypertensive treatment maybe initiated
	SBP >150 mm Hg but <160 mm Hg and / or DBP >100 mm Hg but <105 mm Hg	Continue at the same dose level, and institute new or additional antihypertensive medication if not on maximal antihypertensive treatment, or Reduce by 1 dose level if on maximal antihypertensive treatment.
	SBP >160 mm Hg and / or DBP >105 mm Hg	Hold and adjust antihypertensive medication to achieve BP controlled to SBP ≤150 mm Hg and DBP ≤100 mm Hg. Resume at the same dose level or 1 level reduced. Note: If axitinib dosing is temporarily interrupted, subjects receiving antihypertensive medications should be monitored closely for hypotension. The plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dose interruption.
	Recurrent hypertension following previous dose reduction	Repeat dose interruption and/or dose reduction. ***Permanently discontinue*** if hypertension is severe and persistent despite anti-hypertensive treatments and dose reduction, or experiencing hypertensive crisis, transient or permanent neurological deficit related to uncontrolled hypertension.
Proteinuria	Dipstick negative or 1+	Continue at the same dose level.
	If dipstick shows ≥2+, perform 24-hour urine protein or UPC. Dosing may continue while waiting for test results.	
	Urine protein <3 g/24 hr or UPC <3	Continue at the same dose level.
	Urine protein ≥3 g/24 hr or UPC ≥3	Hold until urine protein is <3 g/24 hr or UPC<3. Restart with 1 dose level lower ***Permanently discontinue*** if urine protein cannot reduce to < 3 g/24 hr or UPC <3 after dose reduced to 2 mg BID
Diarrhea	Grade 1 – 2	Continue at the same does level
	Grade 3	Follow the guidelines as in non-hematologic toxicities
	Grade 4	Follow the guidelines as in non-hematologic toxicities

Toxicity	NCI CTCAE grade	Axitinib
Hemorrhage /Bleeding	Grade 1	For hemoptysis, interrupt study treatment and evaluate underlying causes. Resume at the discretion of the investigator. For other Grade 1 hemorrhage/bleeding events, continue at the current dose; monitor as clinically indicated.
	Grade 2	For pulmonary or GI bleed (other than hemorrhoidal bleeding), ***Permanently discontinue*** and follow-up per protocol. For other Grade 2 hemorrhage/bleeding events, interrupt study treatment until the AE resolves to ≤ Grade 1. Restart at 1 dose level lower
	Grade 3 or 4	***Permanently discontinue*** and follow-up per protocol.
AST/ALT with total bilirubin <2xULN and PT/INR <1.5xULN	Grade 1	Continue at the same dose level
	Grade 2	Hold until recovery to <2xULN or BL. Restart at same dose level.
	Grade 3 or 4	Hold until recovery to <2xULN or BL. Restart at 1 dose level lower.
AST/ALT Elevation with clinically significant hepatic dysfunction (i.e. total bilirubin ≥ 2xULN excluding biliary obstruction or PT/INR ≥ 1.5xULN)		***Permanently discontinue*** and follow-up per protocol. See Section 5.2.2.3.1 for details in evaluating and managing ALT/AST elevations during axitinib/pembrolizumab combination treatment
Hyperthyroidism	Grades 1-2	Continue at the same dose level
	Grade 3	If symptoms can be controlled with symptomatic medications, or if asymptomatic: may continue at the same dose level or dose reduced by 1 dose level per Investigator judgment
	Grade 4	Hold until recovery to Grade ≤ 1 or BL. Restart at 1 dose level lower.
Hypothyroidism	All grades	Axitinib can be continued while thyroid replacement therapy is instituted
Renal Failure or Nephritis	Grade 1-2	Continue at the same dose level
	Grade 3 -4	Hold until recovery to Grade < 2. Restart at 1 dose level lower.

Toxicity	NCI CTCAE grade	Axitinib
Non-hematologic Toxicities, Laboratory Abnormalities and/or Other Drug Related Toxicities suspected to be contributed to axitinib and not considered immune-related	Grade 1 - 2	Continue axitinib at the same dose level
	Grade 3 - 4	Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry (other than abnormal liver test) laboratory abnormalities may continue axitinib at the same dose level per Investigator judgment. Other Grade 3 toxicities may continue axitinib dose reduced by 1 dose level. Grade 4 asymptomatic biochemistry laboratory (other than abnormal liver test) abnormality may continue axitinib without interruption per Investigator's judgment. Other Grade 4 non-hematologic/laboratory and non-laboratory abnormalities hold treatment until recovery to Grade <2 then, then restart axitinib dose reduced by 1 dose level.
	Grade 3- 4 discontinuation criteria	***Permanently discontinue*** axitinib for: • Severe or Grade 3 drug-related AEs that recur • Any life-threatening AEs. • Subjects with the following events will be permanently discontinued: RPLS, arterial thrombosis/ischemia,
Hematologic Laboratory Abnormalities	Grade 1-3	Continue axitinib at the same dose level.
	Grade 4	Hold axitinib until recovery to Grade ≤ 2. Restart axitinib dose reduced by 1 dose level. *Note:* Grade 4 lymphopenia not associated with clinical events, (e.g., opportunistic infection) may continue on with axitinib.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; BL=baseline; BP=blood pressure; DBP=diastolic blood pressure; GI=gastrointestinal; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; SBP=systolic blood pressure; UPC=urine protein creatinine

Allowed Dose Reduction, Interruption and Escalation Levels for Axitinib

The starting dose of axitinib is 5 mg BID. The axitinib dose may be adjusted by a dosing interruption with or without dose reduction as indicated. The dose modification can occur independently for the 2 drugs used in the pembrolizumab plus axitinib arm. If axitinib dose reduction from 5 mg BID is required, the next recommended dose level is 3 mg BID. If further dose reduction is required, the next dose level will be 2 mg BID. Axitinib should be permanently discontinued if subjects cannot tolerate 2 mg BID. The axitinib dose can also be interrupted due to toxicity. Consult with the Sponsor if dose has been interrupted consecutively for more than 3 weeks to determine whether subject may resume axitinib treatment.

Subjects who have tolerated axitinib 5 mg BID for 2 consecutive treatment cycles (i.e. 6 weeks) with no > Grade 2 treatment-related AEs to axitinib and with BP well controlled to ≤ 150/90 mm Hg may have axitinib dose increased to 7 mg BID. Axitinib dose may be further increased to 10 mg BID using the same criteria. Particular attention should be

provided to a subject's overall safety profile prior to implementing intra-subject dose increase for axitinib. See Table 9 for axitinib dose levels.

Table 9 Axitinib Dose Levels

Dose Level	Dose
+2	10 mg BID
+1	7 mg BID
Starting dose	**5 mg BID**
-1	3 mg BID
-2	2 mg BID

5.2.2.3 General Guidance on Evaluation and Management of AEs Potentially Associated with Either Pembrolizumab Axitinib or Both in the Combination Arm

Based on the known toxicity profiles of pembrolizumab and axitinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for axitinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs may be initially considered attributed to either study drugs, such as diarrhea, hypothyroidism, and liver enzyme elevation. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset:

   Since axitinib is dosed BID continuously due to a short half-life, and pembrolizumab is dosed Q3W due to a long half-life, axitinib can be interrupted to assess whether an AE improves/resolves with dechallenge (i.e., interruption of treatment) based on the following two scenarios.

   - If an AE occurs during a treatment cycle (i.e., between 2 pembrolizumab doses), only axitinib dose interruption is needed.
   - If an AE occurs at the beginning of a treatment cycle, axitinib can be interrupted and dosing of pembrolizumab should be held.

   If a subject recovers from an AE in response to axitinib interruption (i.e., positive dechallenge), the event is more likely to be attributed to axitinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE:

   If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting or holding both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

5.2.2.3.1 Evaluation and management of ALT/AST elevations during axitinib and pembrolizumab combination therapy

Based on the existing data from clinical trials, ALT/AST elevations have been observed in advanced cancer patients who received axitinib or pembrolizumab monotherapy treatment. In the Phase 3 study that compared axitinib versus sorafenib in treatment-naïve advanced RCC patients [15], laboratory data showed that the rate of ALT elevation was 40.4% for all grade, 29.8% for Grade 1, 6.7% for Grade 2, 3.9% for Grade 3, and zero for Grade 4. The AE data showed that reported ALT elevation regardless of causality was 10.6% for all grade, 4.8% for Grade 1, 2.6% for Grade 2, 3.2% for Grade 3, and zero for Grade 4. Similar results were observed for AST [unpublished data provided by Pfizer].

Based on data from 2799 subjects with either advanced melanoma or NSCLC treated with pembrolizumab monotherapy, the incidence of immune-mediated hepatitis was 0.7% for all grade, 0.4% for Grade 3, and no Grade 4 or 5 events [Pembrolizumab IB]. In the updated data from an ongoing Phase 1/2 study of axitinib plus pembrolizumab in treatment-naïve advanced RCC, 4 out of 52 subjects had Grade 3 and another 4 had Grade 2 treatment-related ALT/AST elevations or hepatic dysfunction.

Differentiation of whether ALT/AST elevations are attributable to axitinib or pembrolizumab or both may be challenging, as no specific clinical picture or laboratory markers are available. In addition, alternative causes (e.g., viral hepatitis and other severe infections, liver metastasis, ischemia, alcohol intake, etc.) should be excluded before more definitively concluding the attribution of ALT/AST elevation by the study drugs.

For assessing drug-induced liver injury (DILI), the Roussel Uclaf Causality Assessment Method (RUCAM) can be used as a valid tool in which factors like time to onset of ALT/AST elevation, response to drug dechallenge, response to drug rechallenge, evaluation of alternative causes etc. are collectively evaluated and scored to determine the possibility of attribution to ALT/AST elevation [54]. For axitinib, early-onset, prompt recovery from ALT/AST elevation in response to axitinib interruption without confounding by corticosteroid treatment, suggests the event is likely associated with axitinib after excluding other alternative explanations). A positive rechallenge, i.e., ALT/AST recurrence following retreatment will provide further support for its attribution. The determination of immune-related hepatitis mostly relies on the exclusion of other causes including axitinib. If the initial ALT/AST elevation does not respond rapidly to axitinib interruption but responds to subsequent corticosteroid treatment, it suggests a potential for immune-mediated hepatitis by pembrolizumab. It should be borne in mind that not all immune-mediated hepatitis will respond to corticosteroid treatment.

Guidelines on causality evaluation and management for ALT/AST elevations of > 3xULN during axitinib / pembrolizumab combination treatment are outlined in the following:

1. **Promptly interrupt both study drugs and any other suspected concomitant medications.** Note, concomitant medications include over-the-counter (OTC) and herbal medications and supplements.
2. **Adequately monitor liver enzymes and liver function changes** - Liver enzyme tests should include ALT, AST, and ALP; liver function tests should include total bilirubin, and PT or INR. Bilirubin fractionation should be performed if total bilirubin is ≥ 2xULN or is clinically significant as elevated conjugated bilirubin (i.e., direct bilirubin) reflects liver dysfunction. Liver enzyme tests and liver function tests will be referred, collectively, as liver tests for the rest of this section.
    a. Repeat liver tests within 24 to 72 hours to confirm the initial observation.
    b. Continue to monitor liver tests twice weekly, while evaluating other causes, until ALT/AST values are trending down (>10% decrease between sequential assessments) and then monitored weekly until recovered to ≤ 2xULN or values are back to baseline.
3. **Decision on initiation of corticosteroid treatment -** While corticosteroid is essential for managing immune-mediated hepatitis, administration of steroids prior to identifying the most likely causes of ALT/AST elevation will confound the causality assessment and impact proper management of the event. Hence the followings are recommended:
    a. ***Hold steroid initiation*** for ALT/AST elevations that are not associated with signs of clinically significant hepatic dysfunction (i.e., total bilirubin <2xULN and PT/INR <1.5xULN). Continue to monitor with liver tests and clinical symptoms.
    b. ***Steroid therapy should be initiated if:***
        i. ALT/AST elevation is associated with signs of clinically significant hepatic dysfunction (i.e., ALT/AST > 3 x ULN concurrent with total bilirubin ≥2xULN (excluding biliary obstruction) and/or PT/INR ≥1.5xULN) OR,
        ii. ALT/AST elevation has been persistent *(*ie*,* no prompt improvement after axitinib dechallenge) or further increased and without alternative causes identified. Consider observing liver enzyme and function changes for approximately 3 to 7 days prior to making a decision, if subject is clinically stable.
4. **Thoroughly evaluate alternative causes** – The following includes a list of potential alternative causes that should be evaluated and excluded:
    a. Medical history relevant to the liver event
    b. History of alcohol use and recent alcohol use
    c. Serology for hepatitis A, B, C, and E; serology for CMV, EBV

d. Obstructive hepatic disease

e. Cardiac or vascular etiology (e.g., any cause of severe hypoperfusion of the liver, severe cardiac failure)

f. Severe systemic infection

g. Exposure to other drugs including OTC and herbal medications that are potentially associated to DILI (e.g., statins, acetaminophen etc.)

h. Evaluating other causes as appropriate

5. **Decision on axitinib/ pembrolizumab rechallenge** – If initial ALT/AST elevation event is assessed as related to study treatment (*i.e.,* alternative causes were excluded), the decision on rechallenge with one or both study treatments should be based on the outcome of causality assessments (as described above) and the severity of the initial ALT/AST elevation event. Prior to rechallenge with either axitinib or pembrolizumab, initial ALT/AST elevations must recover to ≤ 2 × ULN or to baseline values without signs and symptoms of hepatic dysfunction. See Table 10 for algorithms of decision on axitinib/ pembrolizumab rechallenge after recovery from drug-related ALT/AST elevation.

6. Severe hepatic events should be promptly managed, including hospital admission and seeking hepatic consultation as appropriate.

Table 10 Algorithms of decision on axitinib/ pembrolizumab rechallenge after recovery from drug-related ALT/AST elevation

Initial ALT/AST elevation scenario	**Rechallenge decision**
Scenario 1: ALT/AST > 3 x ULN concurrent with total bilirubin ≥2xULN (excluding biliary obstruction) and/or PT/INR >1.5xULN (i.e., ALT/AST elevation with clinically significant signs of hepatic dysfunction)	• No rechallenge with either axitinib or pembrolizumab is allowed. Subject should be followed with liver tests until recovery..
Scenario 2: ALT/AST >3-5 x ULN without clinically significant signs of hepatic dysfunction (*i.e.* total bilirubin < 2xULN and PT/INR <1.5xULN)	• Axitinib and pembrolizumab combination can be resumed sequentially with axitinib (at the previous dose) resumed first for 2-3 weeks with weekly liver test monitoring: o If no recurrence, consider adding pembrolizumab o If with ALT/AST recurrence is >5xULN (i.e., Grade 3 or 4), discontinue axitinib and rechallenge with pembrolizumab o If ALT/AST recurrence is >3-5xULN (i.e., Grade 2), dose reduce axitinib then rechallenge or discontinue axitinib and rechallenge with pembrolizumab • Permanently discontinue pembrolizumab if ALT/AST recurrence is >5× ULN or interrupt pembrolizumab if ALT/AST recurrence is >3 to 5× ULN after its rechallenge and manage per Section 5.2.2.1.

Initial ALT/AST elevation scenario	Rechallenge decision
Scenario 3: ALT/AST >5 to 10× ULN without clinically significant signs of hepatic dysfunction (i.e., total bilirubin < 2× ULN and PT/INR <1.5× ULN). **Consultation with Sponsor medical monitor is required prior to rechallenge.**	• If initial event is likely to be immune-mediated by pembrolizumab (i.e., no prompt decrease in ALT/AST after axitinib interruption and required initiation of steroid treatment as described in item 3b of this section, responded to steroid treatment, and no alternative explanations): o discontinue pembrolizumab and rechallenge with axitinib as monotherapy (at same dose) • If initial event is likely related to axitinib (e.g. prompt recovery after axitinib interruption without confounding by steroid treatment), first rechallenge with axitinib (at reduced dose) for 2 to 3 weeks with weekly liver test monitoring: o If no recurrence, add pembrolizumab o If ALT/AST recurrence is >5× ULN, permanently discontinue axitinib and rechallenge with pembrolizumab o If ALT/AST recurrence is >3 to 5× ULN, dose reduce axitinib then rechallenge or discontinue axitinib, depending on the reoccurrence of the events and rechallenge with pembrolizumab • Permanently discontinue pembrolizumab if ALT/AST recurrence is >5× ULN or interrupt pembrolizumab if ALT/AST recurrence is >3 to 5× ULN after its rechallenge and manage per Section 5.2.2.1.
Scenario 4: ALT/AST > 10 × ULN without clinically significant signs of hepatic dysfunction **Consultation with Sponsor medical monitor is required prior to rechallenge**	• If initial event is likely to be immune-mediated by pembrolizumab: o discontinue pembrolizumab and rechallenge with axitinib as monotherapy • If initial event is likely related to axitinib and unlikely due to pembrolizumab: o Rechallenge with pembrolizumab monotherapy • If event is potentially related to a contribution of both drugs (such as upfront steroid use with improvement along with axitinib interruption), subject may be rechallenged with axitinib at reduced dose: o If no recurrence, continue with axitinib monotherapy o If ALT/AST elevation recurs, discontinue axitinib and may be rechallenged with pembrolizumab • Permanently discontinue pembrolizumab if ALT/AST recurrence is >5× ULN or interrupt pembrolizumab if ALT/AST recurrence is >3 to 5× ULN after its rechallenge and manage per Section 5.2.2.1. • Permanently discontinue axitinib if ALT/AST recurrence is >5× ULN or interrupt axitinib if ALT/AST recurrence is >3 to 5× ULN and rechallenge with reduced dose.
Note: 1. Subject should have weekly monitoring with liver tests (i.e., liver enzyme and function tests) for 2-3 weeks after each drug rechallenge. 2. If both study drugs are discontinued due to a hepatic event, subjects should be monitored until AE resolution as per protocol and continue imaging and survival follow-up as per protocol. 3. Events under Scenario 1, 3, and 4 must be reported to the Sponsor as Events of Clinical Interest (see Section 7.2.3.2 for details). 4. Liver tests include liver enzyme (ALT, AST, and ALP) and liver function (bilirubin and PT/INR) tests. Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; PT = prothrombin time.	

5.2.2.4 Dose Modification Guidelines for Adverse Events Potentially Associated with Sunitinib Treatment

The study is using the label-recommended dose and schedule for RCC (50 mg QD 4 weeks on, 2 weeks off). Dose interruption and/or dose modification in 12.5-mg increments or decrements is recommended based on individual safety and tolerability, as per label recommendations. If 50 mg QD cannot be tolerated, the next dose level is 37.5 mg QD. Dose can be further reduced to 25 mg QD. Once toxicity has been alleviated, doses should be re-escalated stepwise to 37.5 mg and then 50 mg. Subjects requiring a dose below 25 mg QD should be permanently discontinued from study treatment. During each 6-week cycle, subjects will be off of treatment for 2 weeks. If an additional dose interruption for more than 2 weeks is required, the Sponsor should be consulted (Table 11).

Table 11 Dose Modification Guidelines for AEs Potentially Associated with Sunitinib Treatment

Toxicity	**NCI CTCAE Grade**	**Sunitinib**
Hypertension See Section 5.6.2 for monitoring/management of treatment-related hypertension.	SBP ≤150 mm Hg and / or DBP ≤100 mm Hg	Continue at the same dose level Antihypertensive treatment maybe initiated
	SBP >150 mm Hg but < 160 mm Hg and / or DBP >100 mm Hg but < 105 mm Hg	Continue at the same dose level, and institute new or additional antihypertensive medication if not on maximal antihypertensive treatment, or Reduce by 1 dose level if on maximal antihypertensive treatment.
	SBP >160 mm Hg and / or DBP > 105 mm Hg	Hold dose and adjust antihypertensive medication to achieve BP controlled to SBP ≤150 mm Hg and DBP ≤100 mm Hg. Resume at the same dose level or 1 level reduced. ***Note:*** If sunitinib dosing is temporarily interrupted, subjects receiving antihypertensive medications should be monitored closely for hypotension.
	Recurrent hypertensions following previous dose reduction	Repeat dose interruption and/or dose reduction by one lower dose level. ***Permanently discontinue*** if hypertension is severe and persistent despite antihypertensive treatment and dose interruption, or experience hypertensive crisis, transient or permanent neurological deficit related to uncontrolled hypertension.

Toxicity	NCI CTCAE Grade	Sunitinib
Proteinuria	Dipstick negative or 1+	Continue at the same dose level.
	If dipstick shows ≥ 2+, perform 24-hour urine protein or UPC. Dosing may continue while waiting for test results	
	Urine protein < 3 g/24 hr or UPC < 3	Continue at the same dose level.
	Urine protein ≥ 3 g/24 hr or UPC ≥ 3	Hold until urine protein is < 3 g/24 hr or UPC <3. Restart with 1 dose level lower ***Permanently discontinue*** if urine protein cannot reduce to < 3 g/24 hr or UPC <3 after dose reduced to 25 mg daily
Prolongation of QTc Interval:	480 < QTc < 500 msec	Continue study treatment; monitor as clinically indicated.
	QTc ≥500 msec	***Permanently discontinue*** and follow-up per protocol.
Diarrhea/Colitis	Grade 1-2	Continue at the same does level
	Grade 3	Continue and dose reduce by 1 dose level Follow the guidelines as in non-hematologic toxicities
	Grade 4	Follow the guidelines as in non-hematologic toxicities
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	Grade 1	For hemoptysis, interrupt study treatment and evaluate underlying causes. Resume at the discretion of the investigator. For other Grade 1 hemorrhage/bleeding events, continue at the current dose; monitor as clinically indicated.
	Grade 2	For pulmonary or GI bleed (other than hemorrhoidal bleeding), ***Permanently discontinue*** and follow-up per protocol. For other Grade 2 hemorrhage/bleeding events, interrupt study treatment until the AE resolved to ≤ Grade 1. Restart at 1 dose level lower
	Grade 3 or 4	***Permanently discontinue*** and follow-up per protocol.
Hyperthyroidism	Grades 1-2	Continue at the same dose level
	Grade 3	Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry (other than abnormal liver tests) laboratory abnormalities: may continue at the same dose level or reduce by one dose level per Investigator judgment
	Grade 4	Hold until recovery to Grade ≤ 1 or BL. Restart at 1 dose level lower.
Hypothyroidism	All grades	Dose can be continued while thyroid replacement therapy is instituted
Isolated AST/ ALT or bilirubin elevation	Grade 1	Continue at the same dose level
	Grade 2	Hold until recovery to Grade ≤ 1 or BL. Restart at same dose level.
	Grade 3 or 4	Hold until recovery to Grade ≤ 1 or BL. Restart at 1 dose level lower.
	ALT/AST >3xULN concurrent with total bilirubin > 2xULN (excluding Gilbert syndrome)	***Permanently discontinue*** and perform virology and serology tests to evaluate the causes

Toxicity	NCI CTCAE Grade	Sunitinib
Non-hematologic Toxicities, Laboratory Abnormalities and/or Other Drug Related Toxicities suspected to be contributed to sunitinib	Grade 1 - 2	Continue at the same dose level
	Grade 3 or intolerable grade 2	Withhold dose until toxicity is Grade ≤1 or has returned to BL Resume treatment at the same dose level.[a] If the toxicity recurs with Grade 3 severity (or intolerable Grade 2) at the discretion of the investigator, reduce the dose by 1 level.
	Grade 4	Withhold dose until toxicity is Grade ≤1 or has returned to BL, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.[a]
		Permanently discontinue sunitinib for: • Any life-threatening adverse event. • Subjects with the following events: CHF,[b] pancreatitis, necrotizing fasciitis, nephrotic syndrome and thrombotic microangiopathy), RPLS, and arterial thrombosis/ ischemia • Nausea, vomiting, or diarrhea persist at Grade 3 or 4 despite maximal medical therapy.
Hematologic Laboratory Abnormalities	Grade 1-2	Continue at the same dose level.
	Grade 3	Withhold dose until toxicity is Grade ≤2 or has returned to BL, then resume treatment at the same dose level.[c] If the toxicity recurs with Grade 3 severity, at the discretion of the investigator, reduce the dose by 1 level.
	Grade 4	Withhold dose until toxicity is Grade ≤2 or has returned to BL Restart with 1 dose level lower.[c]

[a] Subjects who develop Grade 3 hypophosphatemia or Grade 4 hyperuricemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator.
[b] Subjects should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Assessment of LVEF should be considered as clinically indicated per sunitinib label and standard of care.
[c] Subjects who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption. Complicated neutropenia includes duration of Grade 4 longer than 7 days or concurrent fever or infection.

5.2.3 Timing of Dose Administration

Study treatments should begin on the day of randomization or within 3 days of randomization in both treatment arms. Study treatments and relevant safety assessments are cycle based. The day that the first dose of study treatment is received by each subject denotes Cycle 1 Day 1 (C1D1).

For the combination arm, each treatment cycle is 21 days, which is based on a Q3W dosing schedule of pembrolizumab. C1D1 of the combination arm should start when the subject can receive the first dose of pembrolizumab. The first dose of axitinib should start on the same day when first dose of pembrolizumab is administered, if possible, or start on the following day. For the sunitinib arm, each treatment cycle is 42 days. Study treatment will continue in 21-day or 42-day cycles, for the combination arm and sunitinib arm, respectively, until study treatments are permanently discontinued for the subject. The clinical visits and assessments are detailed in Section 6 – Trial Flow Chart.

5.2.3.1 Pembrolizumab Administration

Pembrolizumab will be administered on Day 1 of each 21-day cycle (± 3 days) starting on C1D1. Pembrolizumab should be administered after all pre-dose study procedures and assessments have been completed as detailed on the Trial Flow Charts in Section 6. Pembrolizumab should be administered as a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of –5 min and +10 min is permitted (i.e., infusion time is 30 minutes: –5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation and administration of pembrolizumab.

5.2.3.2 Axitinib Administration

Axitinib will be taken orally BID, at approximately the same time in the morning and evening each day with approximately 12 hours between the 2 doses. Axitinib should be taken continuously with exception of dose interruptions due to drug-related AEs or intolerance (see Section 5.2.2).

Axitinib tablets may be administered with or without food. Tablets must not be crushed, split or dissolved and subjects should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing.

Subjects must be instructed that if they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken later up to 3 hours before the next scheduled dose, otherwise, it should be skipped and dosing should resume with subsequent doses as prescribed. Subjects must be instructed to record all doses (missed or vomited doses) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and case report forms (CRFs). If a subject inadvertently takes 1 extra dose during a day, the subject should not take the next dose. A dosing diary will be provided to subjects to record dosing details for axitinib.

5.2.3.3 Sunitinib Administration

The first dose of sunitinib administration denotes C1D1 for each subject. Each treatment cycle of sunitinib is 42 days ± a 3-day window. Within each treatment cycle, sunitinib will be administered orally once daily for 4 weeks and then off treatment for 2 weeks.

Sunitinib can be administered with or without food. Capsules must not be crushed, split, or dissolved and subjects should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing.

Subjects must be instructed that if they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Subjects must be instructed to record all doses (missed or vomited doses) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs. A dosing diary will be provided to subjects to record dosing details for sunitinib.

5.2.3.4 Dosing Schedules with Study Treatment Interruptions

In general, subjects in the combination arm should be maintained on an every 21-day (Q21D) treatment and assessment schedule from C1D1 until both treatment(s) are permanently discontinued. In the events that treatment-related AEs require dose interruption or discontinuation of one study drug only, the other study drug should be continued as scheduled, so as the safety assessments. Sometimes, both drugs need to be withheld for a treatment-related AE until causality is clear or until AE improves. Figure 2 depicts a few dose interruption scenarios that may be encountered in the combination arm.

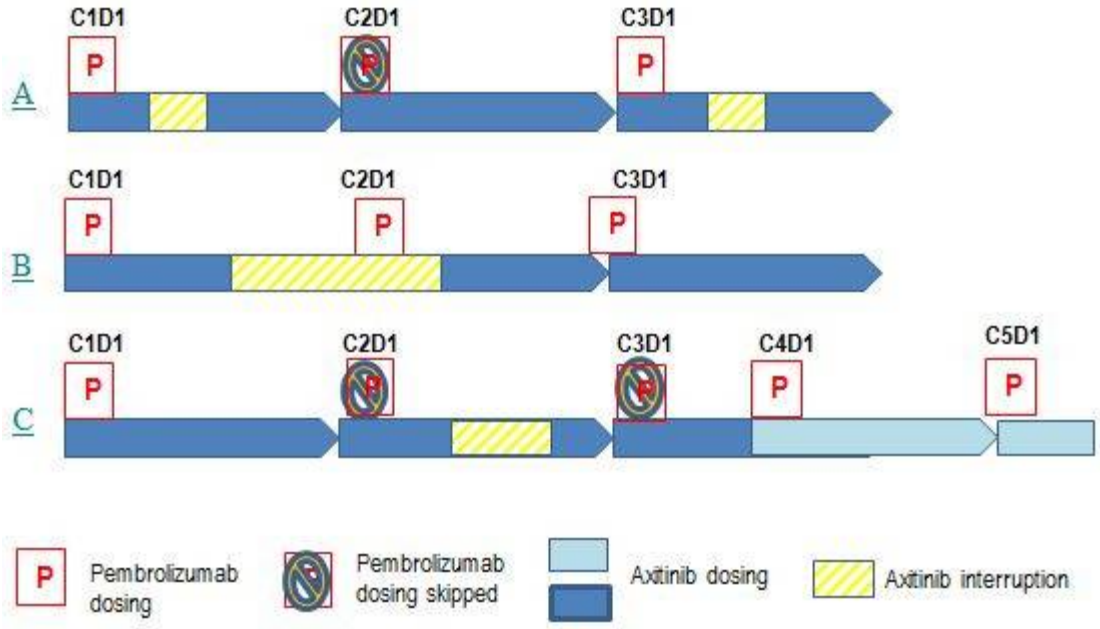


Figure 2 Dose Interruption Scenarios in the Combination Arm

Scenario (A), at C2D1 visit, an immune-related AE is identified that requires pembrolizumab to be on hold but not axitinib, axitinib is then continued. A worsening of hypertension led to brief dose interruption of axitinib during cycle 1 and Cycle 3. Scenario (B), axitinib was interrupted from C1D10 for an axitinib-specific toxicity, subject still comes for C2D1 visit for safety assessment and received Cycle 2 dose of pembrolizumab on schedule. Scenario (C), pembrolizumab has been on hold after Cycle 1 due to a drug-related AE, pembrolizumab can be resumed on C3D10, and the subject may start C4D1 ahead of time and continue the Q21D treatment and safety assessment cycle with this new starting point.

Similarly, subjects who are randomized to the sunitinib arm should be maintained on a 42-day treatment and assessment schedule as much as possible. Figure 3 depicts a few dose interruption scenarios for the sunitinib arm.

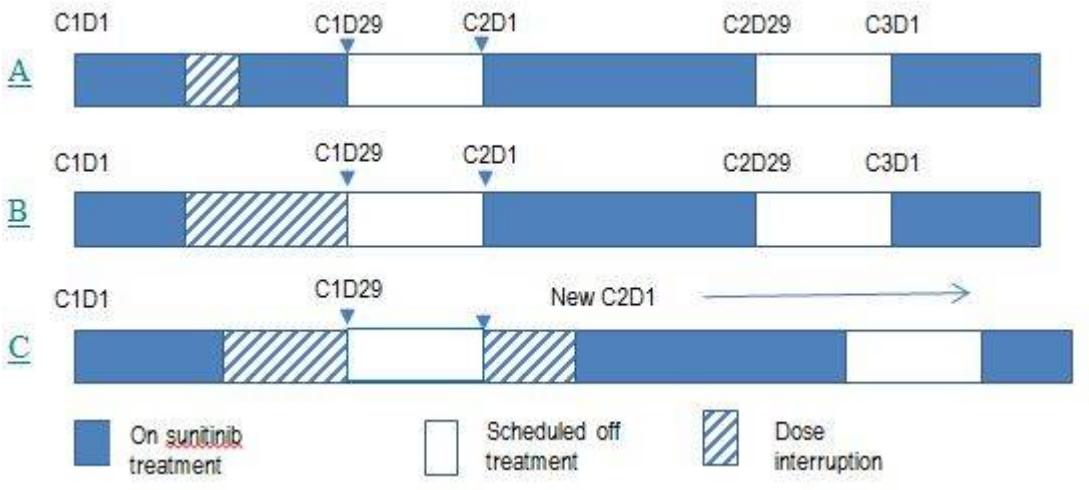


Figure 3 Dose Interruption Scenarios for Sunitinib

(A), if a dose interruption is required within the 28-day treatment period of a cycle, the remaining doses should be completed followed by 2-weeks' off treatment period. (B) If dose interruption extends to the off treatment period and AE resolved, subject should complete the remaining off treatment period and resume treatment at the next cycle per schedule. (C) If dose interruption extends to the treatment period of the following cycle, subject should resume with a new 42-day cycle and continue the 4 weeks on treatment and 2 weeks off treatment schedule and the required assessments.

5.2.4 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization

Treatment randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to the pembrolizumab plus axitinib combination arm or the sunitinib monotherapy arm.

5.4 Stratification

Prior to randomization subjects will be stratified according to the following factors:

1. International Metastatic RCC Database Consortium (IMDC) risk group: favorable versus intermediate versus poor risk groups [2, 3]
2. Geographic region: North America versus Western Europe versus "Rest of the World."

IMDC risk category for each subject is determined first by assessing 6 risk factors as shown in Table 12.

Table 12 IMDC Risk Evaluation

Assessments	Risk Factor
Baseline Karnofsky Performance Status	< 80%
Interval between initial diagnosis of RCC to start of first-line systemic treatment for advanced disease (*note for this study, date of randomization will be used as the start of first-line systemic treatment*)	< 1year
Baseline Hemoglobin	< Lower limit of normal
Baseline Platelet Count	> Upper limit of normal
Baseline Corrected Calcium[1]	> Upper limit of normal
Baseline Neutrophil	> Upper limit of normal
The IMDC risk group is determined by totaling the existing risk factors per subject.	
IMDC Risk Group	**IMDC Category**
Favorable	No risk factors
Intermediate	1 or 2 risk factors
Poor	3 or more risk factors
1. Corrected calcium can be calculated based on the following formula: ***Corrected calcium (mg/dl) = 0.8 × [4.0 - subject's albumin (g/dl)] + subject's calcium (mg/dl)***. A subject's corrected calcium will be compared with the upper limit of normal of institution serum calcium.	

Sites will be provided with a worksheet that utilizes these criteria for calculating the IMDC risk group. The group will be entered into the IVRS as a stratification factor at the time of randomization.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Acceptable Concomitant Medications

- All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

- All medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.
- Concurrent anti-cancer therapy with agents other than those assigned for each treatment arm (i.e., axitinib plus pembrolizumab or sunitinib) is not allowed. Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.5.1.1 Caution Use of Inhibitors and Inducers of CYP Enzymes (Axitinib)

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

The concomitant use of strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs. time curve (AUC) to the range observed without inhibitors. The subsequent doses can be modified based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the axitinib dose should be returned (after 3-5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

5.5.1.2 Caution Use of Inhibitors and Inducers of CYP Enzymes (Sunitinib)

In vitro studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined

(sunitinib + primary active metabolite) C_{max} and AUC0-∞ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors.

CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) maximum concentration (C_{max}) and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's wort) may decrease sunitinib concentrations. St. John's wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers.

The investigator should refer to the approved prescribing information for sunitinib (Sutent) for guidance on permitted medications and non-drug therapies [Sutent Package Insert, 2011].

5.5.1.3 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines [55]. The use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Subjects who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and subjects may start either drug during the study at the discretion of the treating physician.

5.5.2 Concomitant Surgery

Subjects can receive surgical procedures during the study treatment period for indications other than treating RCC.

5.5.2.1 Axitinib

No formal studies of the effect of axitinib on wound healing have been conducted; however, caution is advised based on the mechanism of action. If a major surgery or an interventional procedure (e.g., endoscopy) is required, treatment with axitinib must be interrupted at least 24 hours before the procedure and subject's BP should be monitored closely for hypotension. Subject may resume axitinib 7 days after minor surgery and 2 to 3 weeks after major surgery, provided that the wound has completely healed and there are no wound healing complications (e.g., delayed healing, wound infection or fistula).

5.5.2.2 Pembrolizumab

Dosing interruptions are permitted in the case of surgical events such as elective surgery. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for the interruption should be documented.

5.5.2.3 Sunitinib

Cases of impaired wound healing have been reported during sunitinib therapy. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of re-initiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery [refer to the Sutent Label for details].

5.5.3 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the study treatment period (including re-treatment for post-complete response relapse) of this trial:

- Any anti-cancer therapy not assigned per protocol (e.g., systemic treatment, surgery, radiation).

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered an exception on a case-by-case basis after consultation with Sponsor. The radiation treatment field may not include a target or measurable lesion by RECIST 1.1.

- Investigational agents other than those specified in this protocol (i.e., pembrolizumab, axitinib or sunitinib based on what is assigned)

- Live vaccines within 30 days prior to the first dose of pembrolizumab and through 30 days following the last dose of pembrolizumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

  Note: If precluded by local regulations, live vaccines should not be given for 120 days after the last dose of pembrolizumab is administered.

- Drugs with proarrhythmic potential: Concomitant treatment with a drug having known proarrhythmic risks (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide) is not permitted during treatment with sunitinib.

The following applies exclusively to subjects being treated with pembrolizumab plus axitinib:

- Prolonged therapy with systemic glucocorticoids for any purpose other than to modulate symptoms from an AE, SAE, or ECI or for use as a pre-medication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography. Brief, limited use of systemic corticosteroids (≤7 days) is permitted where such use is considered standard of care (e.g., for COPD exacerbation).

  Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

Subjects who, in the assessment by the investigator, require additional anti-cancer treatments will be discontinued from study treatment and continue on survival follow-up. Subjects who, in the assessment by the investigator, require any other prohibited medications for the assigned study treatment for long-term clinical management should be discontinued from trial treatment but continue on disease assessments and survival follow-up. Subjects may receive other medications that the investigator deems to be medically necessary.

5.6 Rescue Medications & Supportive Care

5.6.1 Management of Treatment-emergent Hypertension

Subjects are encouraged to have home BP monitoring and to measure their BP prior to taking each axitinib or sunitinib dose. All BP measurements will be recorded in a diary and brought to the nurse or study coordinator at each clinic visit. Subjects should contact the site for guidance if their SBP rises above 150 mm Hg, DBP rises above 100 mm Hg, or if they develop symptoms perceived to be related to an elevated BP (e.g., headache, visual disturbance).

Standard anti-hypertensive medications can be used to manage treatment-emergent BP elevation (e.g. thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, and dihydropyridine calcium channel blockers). See Section 5.5 for concomitant medications that are prohibited or should be used with caution.

5.6.2 General Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/ paracetamol to a MAXIMUM total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.
- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low dose heparin cannot be administered, the administration of coumadin or other coumarin derivatives or other anti-coagulants may be allowed; however appropriate monitoring of prothrombin time/International normalized ratio (PT/INR) should be performed.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3. Have a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

1) Practice abstinence[†] from heterosexual activity;

   [†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

   OR

2) Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (1 of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly pregnancy testing is recommended per local standards if applicable.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, axitinib, or sunitinib, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab, axitinib, or sunitinib are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of study treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond study treatment discontinuation are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued study treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the study will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1 – Withdrawal/Discontinuation.

Subjects may discontinue study treatment at any time for any reason or be dropped from study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from study treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue study treatment.

Subjects with AEs meeting discontinuation criteria as described in Section 5.2.1.

- The subject has a medical condition or is non-compliance to study treatments or procedures which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk from continued administration of study drug.
- Female subject with confirmed positive serum pregnancy test.

When a subject is first identified with radiologic PD by the investigator, all scans must be submitted to the central imaging vendor for verification of PD by BICR. Clinically stable subjects may remain on study treatment while waiting for BICR verification and/or have further scans to confirm PD by the site. Details pertaining to BICR verification of PD, confirmation of PD by the site and timing for discontinuation of study treatment due to PD are described in Section 7.1.2.

Subjects in the combination arm must discontinue pembrolizumab after receiving 35 doses of but may continue receiving axitinib until disease progression.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the Trial Flow Chart (Section 6.0), should be completed.

Subjects who discontinue treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol defined schedule until: 1) PD is BICR verified or further confirmed by investigator, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent from trial or 5) study conclusion or early termination, whichever occurs first.

For information about the Safety Follow-up Visit, please refer to Section 7.1.5.3.2.

For information about the Second Course Phase (Retreatment Period), please refer to Section 7.1.5.2.1.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject will be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.8.2.1 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

5.8.3 Second Course Phase (Retreatment)

Subjects enrolled in the pembrolizumab plus axitinib arm who stop pembrolizumab with SD or better may be eligible for up to 17 additional infusions of pembrolizumab therapy if they progress after stopping. This re-treatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

Stops initial treatment with pembrolizumab after a confirmed CR according to RECIST 1.1 per investigator assessment and has received at least 8 doses of pembrolizumab

OR

- Has completed 35 doses (approximately 2 years) of pembrolizumab treatment without PD

AND

- Experiences an investigator-confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Does not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a KPS of $\geq$ 70%
- Demonstrate adequate organ function as detailed in Table 4
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the clinical cutoff for the final OS analysis has been achieved.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. The trial may be stopped early for futility or safety at the recommendation of the eDMC
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
5. Plans to modify or discontinue the development of the study drug
6. In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart (Pembrolizumab in Combination With Axitinib)

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 21 days)[a]**													**End of Treatment**	**Post-Treatment**		
		Cycles 1-8									To be repeated Beyond Cycle 12					Safety Follow-up 30 days from last dose	Imaging Follow-up Q6W or Q12W[b]	Survival Follow-up Q12W[c]
	Screening	C1		C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12				
Scheduled Clinic Visit:		D1[a]	D8	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	End of Treatment			
Clinic Visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	(± 7)	(± 7)
ADMINISTRATIVE PROCEDURES																		
Informed Consent[d]	X																	
Informed Consent - FBR	X																	
Inclusion/Exclusion Criteria	X																	
Subject Identification Card[e]	X														X			
Demographics & Medical History	X																	
Prior and Concomitant Treatment/Medication Review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Post-study Anti-cancer Therapies																X	X	X
Survival Status[g]		<-->																X
STUDY DRUG ADMINISTRATION/COMPLIANCE																		
Pembrolizumab Infusion[h]		X		X	X	X	X	X	X	X	X	X	X	X				
Axitinib Dosing[h]		X (continuous BID dosing)																
Dispense Axitinib and Dosing Diary[i]		X		X	X	X	X	X	X	X	X	X	X	X				
Review Axitinib Compliance[i]				X	X	X	X	X	X	X	X	X	X	X	X			
CLINICAL PROCEDURES/ ASSESSMENTS																		
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	
Full Physical Examination	X														X			
Directed Physical Examination				X	X	X	X	X	X	X	X	X	X	X				
Vital Signs[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial Period:	Screening	Treatment Cycles (1 cycle = 21 days)[a]													End of Treatment	Post-Treatment		
		Cycles 1-8									To be repeated Beyond Cycle 12					Safety Follow-up 30 days from last dose	Imaging Follow-up Q6W or Q12W[b]	Survival Follow-up Q12W[c]
	Screening	C1		C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12				
Scheduled Clinic Visit:		D1[a]	D8	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	End of Treatment			
Clinic Visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	(± 7)	(± 7)
12-Lead ECG[l]	X						X				X					X		
Karnofsky Performance Status[m]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
EFFICACY MEASUREMENTS – TUMOR IMAGING																		
Chest, Abdomen, Pelvis (CAP)	X[n]	X[o]															X[p]	
Bone Scan	X[n,q]	X[q]															X[q]	
Brain Scan	X[n,r]	X[r]															X[r]	
PATIENT-REPORTED OUTCOMES																		
QoL (FKSI-DRS, EORTC QLQ-C30, EQ-5D-3L)[s]		X		X	X	X	X	X	X	X	X		X		X	X		
LABORATORY PROCEDURES/ASSESSMENTS – Local Laboratory																		
Pregnancy Test[t]	X																	
PT/INR[u]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology[u]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry[u]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[u]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
Thyroid Function Testing[u]	X			X	X	X	X	X	X	X	X	X	X	X	X	X		
LABORATORY PROCEDURES/ASSESSMENTS – Central Laboratory																		
PK[v,w]		X			X		X				X					X		
ADA[v]		X			X		X				X					X		
TUMOR BIOPSY/ ARCHIVAL TISSUE COLLECTION/BLOOD FOR CORRELATIVE STUDIES																		
Tumor Tissue Collection	X[x]																	
Blood for genetic analyses[y]		X																
Blood for ctDNA analyses[z]		X		X			X								X			
Blood for TCR repertoire[z]		X		X			X								X			
Blood for RNA analyses[z]		X		X			X								X			

Trial Period:	Screening	Treatment Cycles (1 cycle = 21 days)[a]													End of Treatment	Post-Treatment		
		Cycles 1-8									To be repeated Beyond Cycle 12					Safety Follow-up 30 days from last dose	Imaging Follow-up Q6W or Q12W[b]	Survival Follow-up Q12W[c]
	Screening	C1		C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12				
Scheduled Clinic Visit:		D1[a]	D8	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	End of Treatment			
Clinic Visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	(± 7)	(± 7)
Blood for plasma biomarker analyses[z]		X		X											X			
Blood for serum biomarker		X		X											X			

a. Each treatment cycle in the pembrolizumab plus axitinib arm is 21 days ± 3 days. C1D1 denotes the first dose of study treatment, which can be on the date of randomization or within 3 days of randomization.
b. Imaging follow-up visits are for subjects who have discontinued study treatment without reaching BICR verified or further investigator confirmed PD. See footnotes "n" and "o" for further details.
c. Survival follow-up may be conducted as a telephone call or a clinic visit Q12W (visit window is ± 7 days through Week 104 and ± 14 days after Week 104). Survival contact may be requested more frequently at the time of interim and final analysis or an eDMC safety review (see Section 7.1.5.3.4).
d. Written consent must be obtained prior to performing any protocol-specified procedures.
e. The Subject Identification Card should be dispensed at Screening and collected at the End of Treatment visit.
f. Prior treatments/medications: record **all** prior treatments for RCC. Record all other medications taken within 30 days prior to the first dose of trial treatment. Concomitant medications: enter new medications started during the trial and up to 30 days after last dose of trial treatment regardless of when the Safety Follow-up visit occurs. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.
g. Following verification of disease progression by BICR or further confirmation by the investigator, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
h. Trial treatment should begin within 3 days of randomization for both pembrolizumab and axitinib. See Section 5.2.3 for dose administration details.
i. Subjects will be given a dosing diary for axitinib when axitinib bottles are provided; the dosing diary should be returned at the next visit and be assessed for dosing compliance. See details in Section 7.1.1.9.
j. After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier). See Section 7.2.3.1 for details.
k. Vital Signs will be assessed at Screening (within 10 days of randomization) and D1 of every cycle beginning at Cycle 2, the End of Treatment visit and the Safety Follow-up visit. C1D8 will only collect BP and pulse rate. Height will only be collected at Screening and will be recorded in the vital signs form. See Section 7.1.2.4 for BP assessments at baseline and during treatment.
l. An ECG is performed at Screening (within 10 days of randomization), after the completion of every 4 cycles (12 weeks) on treatment (C5D1, C9D1, C13D1,…) and Safety Follow-up.
m. KPS is assessed at Screening (within 10 days of randomization), on Day 1 visit of every cycle starting from C2 and Safety Follow-up.
n. Baseline imaging must be performed within 28 days prior to randomization. Scans performed as part of routine clinical management are acceptable if they are of

Trial Period:	Screening	Treatment Cycles (1 cycle = 21 days)[a]													End of Treatment	Post-Treatment		
		Cycles 1-8									To be repeated Beyond Cycle 12					Safety Follow-up 30 days from last dose	Imaging Follow-up Q6W or Q12W[b]	Survival Follow-up Q12W[c]
	Screening	C1		C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12				
Scheduled Clinic Visit:		D1[a]	D8	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	End of Treatment			
Clinic Visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	(± 7)	(± 7)

diagnostic quality and within the 28 day window. See Sections 7.1.2.7.1 and 7.1.2.7.2 for additional imaging requirement at baseline and follow up if RCC metastatic lesions identified outside of the standard imaging assessment anatomic regions per protocol.

o. Imaging after randomization will be performed at Week 12 (84 days ±7 days), then Q6W (42 days ±7 days) through Week 54, then Q12W (84 days ±7 days) thereafter until PD is BICR verified. Imaging visit window may be ± 14 days after Week 104. Unscheduled imaging can be performed as clinically indicated. The timing of imaging assessments should follow calendar days from randomization and should not be adjusted for dose delays or cycle starts. Imaging anatomic coverage should be the same as that at screening; see Section 7.1.2.7.2 for details.

p. Subjects who discontinue treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol defined schedule as outlined in footnote "n" until: 1) PD is BICR verified, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion or early termination, whichever occurs first.

q. Baseline bone scan is required for all subjects. If a subject has a positive baseline bone scan, after randomization, bone scans will be performed at Week 18 (Day 126 ± 7 days) and should continue to be performed Q12W (84 days ±7 days) through Week 54, subsequently Q24W (168 days ±7 days) until PD is BICR verified or further confirmed by the investigator. The timing of imaging assessments should follow calendar days from randomization and should not be adjusted for dose delays or cycle starts. Bone scans must be performed for the confirmation of Complete Response (CR) for subjects with a positive bone scan at baseline.

r. A brain scan will be performed during screening for subjects with brain metastasis to ensure subject is stable. After randomization, brain imaging should be performed as clinically indicated and to confirm a CR in subjects with brain metastasis at baseline.

s. At each clinic visit, Quality of Life (QoL) measurements should be performed before all other study procedures and assessments, including the dosing of study medication. QoL will be assessed on D1 visit of every cycle from C1-C8, D1 visit of every other cycle from C9 to C19, D1 visit of every 4 cycles from C19 (approximately Week 54) until study treatment is discontinued. In addition, QoL is to be assessed at the Treatment Discontinuation visit and 30-day Safety follow-up visit. QoL is only assessed once if these two visits are combined.

t. Pregnancy tests – Urine or serum β-hCG: See Section 5.1.2 for pregnancy tests requirements for screening. If the randomization pregnancy test is more than 72 hours prior to the first dose of study treatment, it should be repeated. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Monthly pregnancy testing should be conducted as per local regulations where applicable.

u. PT/INR, hematology, chemistry, urinalysis, and thyroid function testing will be performed at Screening (within 10 days of randomization), on Day 1 visit of every cycle (starting from C2), End of Treatment visit and at the Safety Follow-up visit. Routine safety laboratory values of chemistry and hematology results should be available prior to each pembrolizumab dosing.

v. Pre-dose trough PK and ADA samples for the pembrolizumab plus axitinib arm will be collected on Day 1 of Cycles 1, 3, 5, every 4 cycles thereafter (C9D1, C13D1, C17D1,…) and 30 days after discontinuation. Pre-dose trough samples should be drawn within 24 hours prior to pembrolizumab infusion.

w. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 9. See Section 7.1.3.3 for additional guidance for PK sampling when dosing is interrupted/delayed.

x. Tumor tissue from an archival tissue sample or newly obtained biopsy should be submitted at Screening for biomarker analysis.

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 21 days)[a]**													**End of Treatment**	**Post-Treatment**		
		Cycles 1-8									To be repeated Beyond Cycle 12					Safety Follow-up 30 days from last dose	Imaging Follow-up Q6W or Q12W[b]	Survival Follow-up Q12W[c]
	Screening	C1		C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12				
Scheduled Clinic Visit:		D1[a]	D8	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	End of Treatment			
Clinic Visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	(± 7)	(± 7)

y. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or if the IRB/IEC does not approve) sample collection for these purposes, then such samples will not be collected at the corresponding sites. Leftover DNA extracted from the planned genetic analysis samples will be stored for Future Biomedical Research only if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

z. Blood for ctDNA, TCR repertoire, RNA analyses and blood for serum/plasma biomarker analyses should be collected pre-dose according to time points on the flow chart regardless of missing dose. If visit is skipped, sample should be collected at the next visit. Leftover samples may be kept for Future Biomedical Research if the subject signs the FBR consent.

6.2 Trial Flow Chart (Sunitinib)

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 42 days)[a]**											**End of Treat-ment**	**Post-Treatment**		
		Cycles 1-4									To be repeated Beyond Cycle 6					
Treatment Cycle:	Screening	C1			C2		C3		C4		C5	C6	Discon	Safety Follow-up	Imaging Follow-up	Survival Follow-up
Scheduled clinic visit:		D1[a]	D15	D29	D1	D29	D1	D29	D1	D29	D1	D1		30 days from last dose	Q6W or Q12W[b]	
Clinic visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment	(± 3 days)	(± 7 days)	Q12W[c] (± 7 days)
ADMINISTRATIVE PROCEDURES																
Informed Consent[d]	X															
Informed Consent - FBR (optional)	X															
Inclusion/Exclusion Criteria	X															
Subject Identification Card[e]	X												X			
Demographics & Medical History	X															
Prior and Concomitant Treatment/Medication Review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Post-study Anti-cancer Therapy Status														X	X	X
Survival Status[g]		<--->														X
STUDY DRUG ADMINISTRATION/ COMPLIANCE																
Sunitinib Dosing[h]		X [scheduled dosing is 4 weeks on (D1-D28) and 2 weeks off (D29-D42) for each cycle] from C1D1														
Dispense Sunitinib and Dosing Diary[i]		X			X		X		X		X	X				
Review Sunitinib Compliance[i]					X		X		X		X	X	X			

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 42 days)[a]**											**End of Treat-ment**	**Post-Treatment**		
		Cycles 1-4									To be repeated Beyond Cycle 6					
Treatment Cycle:	Screening	C1			C2		C3		C4		C5	C6	Discon	Safety Follow-up	Imaging Follow-up	Survival Follow-up
Scheduled clinic visit:		D1[a]	D15	D29	D1	D29	D1	D29	D1	D29	D1	D1		30 days from last dose (± 3 days)	Q6W or Q12W[b] (± 7 days)	Q12W[c] (± 7 days)
Clinic visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment			
CLINICAL PROCEDURES/ ASSESSMENTS																
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	
Full Physical Examination	X												X			
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X				
Vital Signs[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG[l]	X						X				X			X		
KPS[m]	X			X	X	X	X	X	X		X	X		X		
EFFICACY MEASUREMENTS – TUMOR IMAGING																
Chest, Abdomen, Pelvis	X[n]	X[o]													X[p]	
Bone Scan	X[n,q]	X[q]													X[q]	
Brain Scan	X[n,r]	X[r]													X[r]	
PATIENT REPORTED OUTCOMES																
QoL (FKSI-DRS, EORTC QLQ-C30, EQ-5D-3L)[s]		X		X	X	X	X	X	X	X	X	X	X	X		
LABORATORY PROCEDURES/ ASSESSMENTS – Local Lab																
Pregnancy Test[t]	X															
PT/INRu[t]	X			X	X	X	X	X	X		X	X	X	X		
Hematology[u]	X			X	X	X	X	X	X		X	X	X	X		
Chemistry[u]	X			X	X	X	X	X	X		X	X	X	X		
Urinalysis[u]	X			X	X	X	X	X	X		X	X	X	X		
Thyroid Function Testing[u]	X			X	X	X	X	X	X		X	X	X	X		

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 42 days)[a]**											**End of Treat-ment**	**Post-Treatment**		
		Cycles 1-4									To be repeated Beyond Cycle 6					
Treatment Cycle:	Screening	C1			C2		C3		C4		C5	C6	Discon	Safety Follow-up	Imaging Follow-up	Survival Follow-up
Scheduled clinic visit:		D1[a]	D15	D29	D1	D29	D1	D29	D1	D29	D1	D1		30 days from last dose (± 3 days)	Q6W or Q12W[b] (± 7 days)	Q12W[c] (± 7 days)
Clinic visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment			
TUMOR BIOPSY/ ARCHIVAL TISSUE COLLECTION/ BLOOD FOR CORRELATIVE STUDIES																
Tumor Tissue Collection	X[v]															
Blood for genetic analyses[w]		X														
Blood for ctDNA analyses[x]		X		X			X						X			
Blood for TCR repertoire[x]		X		X			X						X			
Blood for RNA analyses[x]		X		X			X						X			
Blood for plasma biomarker analyses[x]		X		X									X			
Blood for serum biomarker analyses[x]		X		X									X			

a. Each treatment cycle in the sunitinib arm is 6 weeks long (42 days ± 3 days). C1D1 denotes the first dose of study treatment, which can be on the date of randomization or within 3 days of randomization. See Section 5.2.3.4 for scenarios regarding dose interruptions.

b. Imaging Follow-up visits are for subjects who have discontinued study treatment without reaching BICR verified or further investigator confirmed PD. See footnotes "n" and "o" for further details.

c. Survival Follow-up may be conducted as a telephone call or a clinic visit Q12W (visit window is ± 7 days through Week 104 and ± 14 days after Week 104). Survival contact may be requested more frequently at the time of interim and final analysis or an eDMC safety review (see Section 7.1.5.3.4).

d. Written consent must be obtained prior to performing any protocol-specified procedures.

e. The Subject Identification Card should be dispensed at Screening and collected at the End of Treatment visit.

f. Prior treatments/medications: record **all** prior treatment for RCC. Record all medications taken within 30 days prior to the first dose of trial treatment. Concomitant medications: enter new medications started during the trial and up to 30 days after last dose of trial treatment regardless of when the safety follow-up visit occurs. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

g. Following verification of disease progression by BICR or further confirmation by the investigator, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

h. Trial treatment should begin within 3 days of randomization for sunitinib. See Section 5.2.3 for dose administration details.

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 42 days)[a]**											**End of Treat-ment**	**Post-Treatment**		
		Cycles 1-4									To be repeated Beyond Cycle 6					
Treatment Cycle:	Screening	C1			C2		C3		C4		C5	C6	Discon	Safety Follow-up	Imaging Follow-up	Survival Follow-up
Scheduled clinic visit:		D1[a]	D15	D29	D1	D29	D1	D29	D1	D29	D1	D1		30 days from last dose (± 3 days)	Q6W or Q12W[b] (± 7 days)	Q12W[c] (± 7 days)
Clinic visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment			

i. Subjects will be given a dosing diary for sunitinib when sunitinib bottles are provided; the diary should be returned at the next visit and assessed for dosing compliance. See details in Section 7.1.1.9.
j. After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier). See Section 7.2.3.1 for details.
k. Vital Signs will be assessed at Screening (within 10 days of randomization), Day 15 and Day 29 of C1 and Day 1 and Day 29 C2 to C4, then Day 1 of all subsequent visits, the End of Treatment visit and the Safety Follow-up visit. C1D15 will only collect BP and pulse rate. Height will only be collected at Screening and will be recorded in the vital signs form. See Section 7.1.2.4 for BP assessments at baseline and during treatment.
l. An ECG is performed at Screening (within 10 days of randomization), after the completion of every 2 cycles (12 weeks) on treatment (C3D1, C5D1, C7D1, C9D1,…) and Safety Follow-up.
m. KPS is assessed at Screening (within 10 days of randomization), on Day 29 of C1, Day 1 and D29 of cycle C2-C3, Day 1 of every cycle thereafter (C4D1, C5D1, C6D1,…) and Safety Follow-up.
n. Baseline imaging must be performed within 28 days prior to randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within the 28 day window. See Section 7.1.2.7.1 for additional imaging requirements at baseline and follow-up in subjects with RCC metastatic lesions identified outside of the standard imaging assessment anatomic regions per protocol.
o. Imaging after randomization will be performed at Week 12 (84 days ± 7 days), then Q6W (42 days ±7 days) through Week 54, then Q12W (84 days ±7 days) thereafter until PD is BICR verified or further confirmed by the investigator. Imaging visit window can be ± 14 days after Week 104. Unscheduled imaging can be performed as clinically indicated. The timing of imaging assessments should follow calendar days from randomization and should not be adjusted for dose delays or cycle starts. Imaging anatomic coverage should be the same as that at screening; see Section 7.1.2.7.2 for details.
p. Subjects who discontinue treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol defined schedule as outlined in footnote n until: 1) PD is BICR verified or further confirmed by investigator, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion or early termination, whichever occurs first. See footnote B for Imaging Follow-up schedule and windows.
q. Baseline bone scan is required for all subjects. If a subject has a positive baseline bone scan, after randomization, bone scans will be performed at Week 18 (126 days ± 7 days)and should continue to be performed Q12W (84 days ±7 days) through Week 54. After Week 54, subsequently Q24W (168 days ±7 days) through Week 54 until PD is BICR verified or further confirmed by investigator. The timing of imaging assessments should follow calendar days from randomization and should not be adjusted for dose delays or cycle starts. Bone scans must be performed for the confirmation of Complete Response (CR) for subjects with a positive bone scan at baseline.
r. A brain scan will be performed during screening for subjects with brain metastasis to ensure subject is stable. During the trial, brain imaging should be performed as clinically indicated and to confirm a CR in subjects with brain metastasis at baseline.

Trial Period:	**Screening**	**Treatment Cycles (1 cycle = 42 days)[a]**											**End of Treat-ment**	**Post-Treatment**		
		Cycles 1-4									To be repeated Beyond Cycle 6					
Treatment Cycle:	Screening	C1			C2		C3		C4		C5	C6	Discon	Safety Follow-up	Imaging Follow-up	Survival Follow-up
Scheduled clinic visit:		D1[a]	D15	D29	D1	D29	D1	D29	D1	D29	D1	D1		30 days from last dose (± 3 days)	Q6W or Q12W[b] (± 7 days)	Q12W[c] (± 7 days)
Clinic visit Windows (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment			

s. At each clinic visit, Quality of Life (QoL) measurements should be performed before all other study procedures and assessments, including the dosing of study medication. QoL will be assessed D1 and D29 visits of C1-C4; D1 visit of C5 to C10, and D1 visit of every other cycle from C10 (D1C10, D1C12) (approximately Week 54) until study treatment is discontinued. In addition, QoL is to be assessed at the Treatment Discontinuation visit and 30-day Safety Follow-up visit. QoL is only assessed once if these two visits are combined.

t. Pregnancy tests – Urine or Serum β-hCG: See Section 5.1.2 for pregnancy tests requirements for screening. If the randomization pregnancy test is more than 72 hours prior to the first dose of trial treatment, it should be repeated. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Monthly pregnancy testing should be conducted as per local regulations where applicable.

u. PT/INR, hematology, chemistry, urinalysis and thyroid function testing will be performed at Screening (within 10 days of randomization), C1D29, C2D1, C2D29, C3D1, C3D29, Day 1 of every cycle thereafter (C4D1, C5D1, C6D1,…), the End of Treatment visit and the Safety Follow-up visit.

v. Tumor tissue from an archival tissue sample or newly obtained biopsy should be submitted at screening for biomarker analysis.

w. Samples should be collected for planned analysis of the association between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or if the IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic samples will be stored for Future Biomedical Research only if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

x. Blood for ctDNA, TCR repertoire, RNA analyses and blood for serum/plasma biomarker analyses should be collected pre-dose according to time points on the flow chart. Leftover samples may be kept for Future Biomedical Research if the subject signs the FBR consent.

6.3 Trial Flow Chart Second Course Phase (Retreatment)

Second course re-treatment subjects may receive up to 17 cycles (approximately 1 year) of pembrolizumab therapy.

Trial Period:	**Treatment Cycles**												**End of Treatment**	**Post-Treatment**		
	Cycles 1-8								To be repeated Beyond 12 Cycles							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Imaging Follow-up Visits	Survival Follow-up
Scheduling Window (Days):	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
ADMINISTRATIVE PROCEDURES																
Re-treatment Criteria	X															
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration	X[a]	X	X	X	X	X	X	X	X	X	X	X				
Post-study Anti-cancer Therapy Status															X	X
Survival Status[b]	<--->															X
CLINICAL PROCEDURES/ASSESSMENTS																
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	
Full Physical Examination													X			
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Karnofsky Performance Status[e]	X	X	X	X	X	X	X	X	X	X	X	X	X			
EFFICACY MEASUREMENTS																
Tumor Imaging - chest, abdomen, pelvis (CAP)	X[f]														X[g]	
Tumor Imaging – bone scan	X[f,h]														X[h]	
Tumor Imaging – brain scan	X[i]														X[i]	
LABORATORY PROCEDURES/ASSESSMENTS: ANALYSIS PERFORMED BY LOCAL LABORATORY																
Pregnancy Test – Urine or Serum β-hCG[j]	X															
PT/INR	X[k]															
Hematology[l]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial Period:	Treatment Cycles												End of Treatment	Post-Treatment		
	Cycles 1-8								To be repeated Beyond 12 Cycles							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Imaging Follow-up Visits	Survival Follow-up
Scheduling Window (Days):	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
Chemistry[l]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[m]	X[k]	X		X		X		X		X		X	X	X		
T3, FT4, and TSH[m]	X[k]	X		X		X		X		X		X	X	X		

a. Cycle 1 re-treatment must be given within 3 days.
b. Following documented disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded)..
c. After the end of treatment each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier). See Section 7.2.3.1 for details.
d. Height will be measured prior to re-treatment. Vital signs will be performed within 10 days prior to the first re-treatment dose of pembrolizumab.
e. Karnofsky Performance Status will be performed prior to re-treatment (within 10 days prior to the first re-treatment dose of pembrolizumab) and Day 1 visit of every cycle.
f. The initial tumor imaging will be performed within 28 days prior to first re-treatment cycle and then every 12 weeks thereafter (84 days ±7 days).
g. Subjects who discontinue treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol defined schedule until 1) PD is BICR verified or further confirmed by the investigator, 2) initiation of a new anti-cancer treatment, 3) death or 4) withdraw of consent from trial or 5) study conclusion or early termination, whichever occurs first.
h. A bone scan will be performed prior to first re-treatment cycle. If a subject has a positive bone scan, bone scans will be performed additionally every 24 weeks thereafter (168 days ±14 days). The timing of imaging assessments should follow calendar days from C1 of re-treatment and should not be adjusted for dose delays or cycle starts. Bone scans must be performed for the confirmation of Complete Response (CR).
i. A brain scan is as clinically indicated but is required for subjects with brain metastasis if the subject achieves a CR.
j. For women of childbearing potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial re-treatment. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Monthly pregnancy testing should be conducted as per local regulations where applicable.
k. Laboratory tests for determining eligibility are to be performed within 10 days prior to the first re-treatment dose of pembrolizumab.
l. Hematology and chemistry assessments will be performed prior to re-treatment, Day 1 visit of every cycle, at treatment discontinuation, and 30 days after discontinuation.
m. Urinalysis and T3, FT4, and TSH will be performed prior to re-treatment, then every other cycle starting at Cycle 2, at treatment discontinuation, and 30 days after discontinuation.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will include all active conditions and any conditions diagnosed within the prior 10 years that are considered clinically significant by the Investigator. Details pertaining to the subject's renal cell carcinoma diagnosis will be recorded separately and not listed as medical history.

7.1.1.4.1 History of Renal Cell Carcinoma

The investigator or qualified designee will obtain information regarding the subject's renal cell carcinoma. This information will include but is not limited to the presentation at primary diagnosis, date and stage at primary diagnosis, date of most recent recurrence, and location of metastases at screening (if applicable).

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the subject within 30 days before the first dose of trial medication. Prior treatment for RCC will be recorded separately and not listed as prior medication.

7.1.1.5.2 Prior Treatment Details for Renal Cell Carcinoma

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgeries and record in the trial database on forms specific for each topic.

7.1.1.5.3 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial and until 30 days after the last dose of trial treatment regardless of when the safety follow-up visit occurs. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Subsequent Anti-Cancer Therapy Status

All new anti-cancer therapy initiated after the study start must be recorded in the eCRF. If a subject initiates another anti-cancer therapy other than the assigned study treatment(s), the study treatment(s) should be discontinued and the subject will move into the survival follow-up phase; if a subject initiates a new anti-cancer therapy within 30 days after the last dose of the trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy.

7.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.9 Trial Compliance (Medication)

Interruptions from the protocol specified treatment for pembrolizumab greater than 3 weeks for events unrelated to study therapy or 12 weeks for toxicities, interruptions for axitinib greater than 3 weeks for toxicities, or interruptions for sunitinib greater than 2 weeks beyond the scheduled off treatment portion (2 weeks) at the end of the cycle, require consultation

between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of pembrolizumab will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance to each dose administered. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

Each subject will be dispensed a dosing diary for axitinib and sunitinib. The diary will record the date and time (if applicable) of daily dose, the tablets or capsules taken of each strength dispensed, the blood pressure (if subject is doing home blood pressure monitoring), whether the dose was vomited or missed and any comments regarding missed doses. Compliance with axitinib and sunitinib treatment will be reviewed at each visit for the dose prescribed and dose taken based on the diary.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs must be reported through 30 days following the last dose of trial treatment and should be recorded regardless of when the Safety Follow-up visit occurs. All SAEs must be reported through 90 days following the last dose of trial treatment or until the start of new anti-cancer treatment, whichever comes first. Drug related AEs must be reported regardless of seriousness and whether or not they occur outside of any reporting timeframes.

7.1.2.2 Full Physical Examination

The investigator or clinical designee will perform a complete (full) PE during the screening period and at discontinuation of treatment, as specified in the Trial Flow Chart in Section 6.0. Full physical examination includes a review of the patient's history, evaluation of the patient's general appearance, and examination of the major systems, including cardiovascular, pulmonary, GI, musculoskeletal, lymphatic, and neurologic. Clinically significant abnormal findings at screening should be recorded as medical history. After randomization, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Directed Physical Exam

Other than the Screening and End of Treatment visit, the investigator or qualified designee will perform a directed physical exam as specified in the Trial Flow Charts in Section 6.0. Directed PE refers to a symptoms-directed PE. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Vital Signs

The investigator or qualified designee will assess vital signs (including weight, temperature, pulse rate, respiratory rate, and blood pressure) prior to administration of study treatment at each visit as specified in the Trial Flow Charts for each treatment arm in Section 6.0. Blood pressure should be taken after the subject has been at rest for 10 minutes. At baseline assessments, BP measurements should be performed in triplicate, at least 2 minutes apart. Eligibility should be based on the mean systolic and/or diastolic BP values (see Section 5.1.3, Exclusion Criterion 19). At visits following randomization, triplicate BP measurement is required only if initial BP assessment has SBP $\geq$ 150 mmHg and/or DBP $\geq$ 90 mmHg. In that situation, dose modification should be based on the mean systolic and/or diastolic BP values if associated with study treatment and all 3 measurements are to be entered into the eCRF.

7.1.2.5 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the Trial Flow Chart in Section 6.0. Clinically significant abnormal findings at screening should be recorded in the medical history. Additional ECGs may be performed as clinically necessary.

7.1.2.6 Karnofsky Performance Status

The KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks, with scores ranging from 0% to 100%. A higher score means the patient is better able to carry out daily activities. See Section 12.4 for a description of the full scale. The KPS will be assessed as specified in the Trial Flow Charts in Section 6.0. A KPS $\geq$70% is required for study eligibility.

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the blinded central imaging vendor (CIV) can be found in the Site Imaging Manual (SIM). Acceptable imaging modalities for each anatomic region are described as follows:

- For chest, abdomen and pelvis, CT is the strongly preferred modality and should be acquired with IV and oral contrast. An MRI with IV contrast should only be used when CT is contraindicated. For subjects with renal impairment, the following choices may be selected at the discretion of the investigator: 1) CT without IV contrast for all three anatomic regions or 2) a combination of MRI with or without IV contrast for abdomen and pelvis plus a chest CT without IV contrast.
- For brain metastasis, MRI is preferred but CT is also acceptable.
- For bone metastasis, bone scintillation or local standard of care modality should be used. X-ray may also be taken for symptomatic sites even if bone scan is negative and there is clinical suspicion for metastatic disease.

The same imaging technique regarding modality and use of contrast should be used in a subject for each anatomic region throughout the trial to optimize the visualization of existing and new tumor burden.

All scheduled images for all subjects must be submitted to the designated CIV for BICR review. Imaging (including other modalities) obtained to determine disease progression at unscheduled time points must also be submitted to CIV. In addition, imaging obtained for other reasons but capturing radiologic progression, should also be submitted to CIV for BICR review.

BICR will verify PD following the first radiologic evidence of PD identified by the investigator. BICR PD verification will be expedited and will be communicated to the study site and sponsor (See Section 7.1.2.7.6).

7.1.2.7.1 Tumor Imaging at Screening

Tumor imaging at screening must be performed within 28 days prior to the date of randomization. For this study, imaging of the chest, abdomen, and pelvis (CAP) are required for all subjects at Screening. A subject must have measurable disease per RECIST 1.1 as determined by the investigator at baseline in order to be eligible. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the sponsor allows maximum of 10 target lesions in total and maximum of 5 per organ to be selected at baseline, if clinically relevant, to enable a broader sampling of tumor burden.

Bone scans will be acquired for all subjects at baseline. Additionally, an X-ray may also be taken for symptomatic sites even if bone scan is negative and there is clinical suspicion for metastatic disease.

Subjects with stable brain metastases may participate if they are stable without evidence of progression for at least 4 weeks by repeat imaging. Please note that the repeat imaging should be performed during study screening (see Section 5.1.3 Exclusion 9 for detailed requirement).

Imaging scans performed as part of routine clinical management are acceptable as screening tumor imaging if they are of diagnostic quality, complete and performed within 28 days prior to the date of randomization and can be assessed by BICR.

If a subject has RCC metastatic lesions identified outside of the aforementioned regions, additional imaging of the corresponding anatomic region should also be acquired. For example, if metastases occurred in the head and/or neck area, a soft tissue head and/or neck CT or MRI should be acquired. These lesions can be selected as target or non-target lesions per RECIST 1.1. See Section 7.1.2.7.2 on follow up of these lesions.

7.1.2.7.2 Tumor Imaging During the Trial

Details regarding imaging collection timepoints are provided in the Trial Flow Charts (Section 6.0).

The first post-randomization imaging assessment of CAP will be performed at Week 12 (84 days ± 7 days from the date of randomization). Subsequent tumor imaging of CAP should be performed Q6W (42 days ±7 days) through Week 54 and Q12W (84 days ±7 days)

thereafter until PD is verified by BICR or further confirmed by the investigator. The imaging visit window can be ± 14 days after Week 104. Unscheduled imaging can be performed as clinically indicated. For RCC metastatic lesions identified outside of the protocol-defined regions (i.e., CAP, bone, brain), the lesions should be followed in accordance with the same imaging assessment schedule as CAP and same modality should be used before and after randomization.

If a subject has a positive bone scan at baseline (Screening), post randomization bone scans should be performed at Week 18 (126 days ± 7 days) and then Q12W (84 days ±7 days) through Week 54. After Week 54, bone scans will be performed every 24 weeks (168 days ±7 days). A bone scan may also be obtained if there are new symptoms of bone pain in subjects with negative bone scans at baseline. Additionally, an X-ray may also be taken for symptomatic sites even if the bone scan is negative and there is clinical suspicion for metastatic disease. For subjects with equivocal bone lesions at baseline, the bone scan should be performed in accordance with the aforementioned schedule until the lesions are determined to be non-cancerous.

The timing of imaging assessments should follow calendar dates and should not be adjusted for dose delays or cycle starts.

Imaging should continue until PD is verified by BICR or further confirmed by investigator (i.e., following PD verification by BICR), initiation of a new anti-cancer treatment, death, withdrawal of consent or study conclusion/ early termination, whichever occurs first.

All supplemental imaging must be submitted to the central imaging vendor for BICR.

When PD is first identified by the investigator/local radiologist for a subject, based on imaging assessment, the site should submit all the scans for the subject for an expedited verification of radiologic PD by BICR. The outcome of PD verification by BICR will be communicated to the study site and sponsor and the investigator should decide the next steps as outlined in Section 7.1.2.7.6.

Per irRECIST (Section 7.1.2.7.6), disease progression should be confirmed by the site in clinically stable subjects ≥ 4 weeks after BICR verification of site-assessed first radiologic evidence of PD. Subjects who have unconfirmed PD may continue on treatment at the discretion of the investigator until progression is confirmed by the site and provided that subjects have met the conditions detailed in Section 7.1.2.7.6. Subjects who obtain a confirmation scan do not need to undergo the next scheduled imaging if it is scheduled < 4 weeks after the confirmation scan. Subjects will return to their regular imaging schedule starting with the next timepoint. Subjects who have confirmed disease progression (as assessed by the site) will discontinue treatment. Exceptions are detailed in Section 7.1.2.7.6.

In the event that a subject has experienced a PR or CR, confirmation of response should be performed at the next scheduled imaging assessment visit. For subjects who are enrolled with baseline brain metastases, brain imaging should be performed at confirmation of a CR. Bone scans must also be performed for the confirmation of a CR for those subjects who have a positive bone scan at baseline.

7.1.2.7.3 End of Treatment and Follow-up Tumor Imaging

Subjects who discontinue treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol-defined schedule until PD is BICR verified or further confirmed by investigator (i.e., following PD verification by BICR), initiation of a new anti-cancer treatment, death, withdrawal of consent or study conclusion/early termination, whichever occurs first. See Section 7.1.5.3.3 for more details.

7.1.2.7.4 Second Course (Retreatment) Tumor Imaging

A subject who is eligible for the second course must have baseline imaging (CAP and bone scan) performed within 28 days prior to restarting treatment with pembrolizumab. A local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All second course imaging will be submitted to BICR for retrospective review.

The first on study imaging assessment (CAP) should be performed at Week 12 (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed Q12W (84 days ±7 days) or more frequently if clinically indicated.

A bone scan will be performed prior to first re-treatment cycle and then Q24W thereafter (168 ± 14 days) for subjects with positive bone scan at the start of re-treatment. Brain scan is as clinically indicated. For subject with known brain metastasis, a brain scan is required to confirm a CR.

Imaging should continue until disease progression, initiation of a new anti-cancer treatment, death, withdrawal of consent or study conclusion/ early termination, whichever occurs first.

Per irRECIST (Section 7.1.2.7.6), if tumor imaging shows initial PD, the tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ± 7 days) until: 1) the start of new anti-cancer treatment, 2) disease progression, 3) death or 4) the end of the study, whichever occurs first.

7.1.2.7.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the BICR and the investigator as the primary method for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

Initial tumor imaging showing site-assessed PD should be submitted for BICR immediately. The site will be notified if BICR verifies PD using RECIST 1.1. The upper portion of Figure 4 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.7.6 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs and therefore is only required for subjects in the combination arm. For subjects in the sunitinib treatment arm, irRECIST is optional. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by BICR review will be evaluated retrospectively.

After PD has been verified by BICR, subjects should continue study treatment, if feasible, until progression is further confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In subjects who have shown initial evidence of radiological PD by RECIST 1.1 as verified by BICR, it is at the discretion of the Principal Investigator whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 13 and Figure 4). This clinical decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects who are clinically stable may continue receiving study treatment until PD is confirmed by repeat imaging assessment. Tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
2) No decline in KPS
3) Absence of rapid progression of disease
4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Any subject deemed **clinically unstable** should be discontinued from trial treatment after BICR verification of site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Target lesion sum of diameters is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat imaging does not confirm PD per irRECIST as assessed by the local site investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Target lesion sum of diameters remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy.

NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue pembrolizumab treatment for subjects in the combination arm may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.0 - Trial Flow Chart and be submitted to BICR.

Additional details about irRECIST are referenced in the Merck TIP Sheet for RECIST 1.1 and irRECIST.

Table 13 Imaging and Treatment After First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1 which has been verified by BICR	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment Exception: treatment with pembrolizumab may continue following consultation with the Sponsor if there is no further increase in the tumor burden at the confirmatory tumor imaging,	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

Abbreviations: BICR=blinded independent central imaging review; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

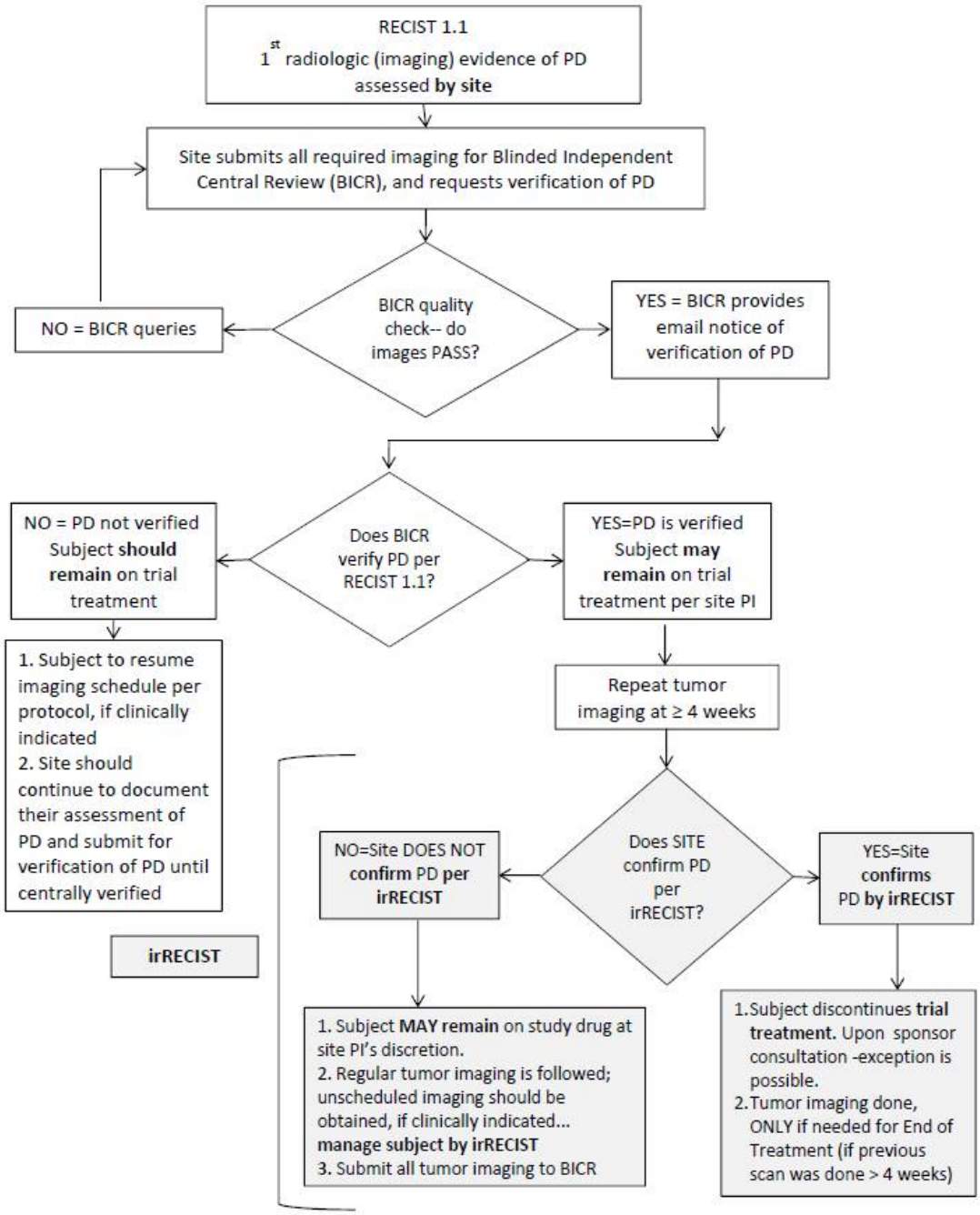


Figure 4 Imaging and Treatment for Clinically Stable Subjects after First Radiologic Evidence of PD Assessed by the Site

7.1.2.8 Patient-reported Outcomes

The FKSI-DRS, EORTC-QLQ-C30 and EuroQol EQ-5D-3L questionnaires will be administered by trained site personnel and completed electronically by subjects in the

following order: FKSI-DRS first, EORTC-QLQ-C30, and then EuroQol EQ-5D-3L at the time points specified in the Trial Flow Chart. It is a best practice and strongly recommended that ePROs are administered to randomized subjects prior to all procedures and assessments, including the dosing of study treatment. If the subject does not complete the PROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed. A visit window of ±7 days will apply to PRO visit assessments. The timing of QoL assessments should not change on the basis of dosing delays or interruptions.

7.1.2.8.1 FKSI-DRS

The FKSI-DRS is a patient-reported instrument that measures whether the patient has experienced any of the following 9 kidney cancer-related symptoms: lack of energy, fatigue, weight loss, pain, bone pain, shortness of breath, cough, fever, or blood in the urine [51]. Each item is scored by using the following 5 response categories: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. Responses to all FKSI-DRS items are summed to generate a summary symptom score ranging from 0 to 36, with higher scores indicating improved (more favorable) symptom status. The FKSI-DRS is a reliable, valid, and responsive brief index of the most important symptoms associated with advanced kidney cancer [51]. This assessment will be completed at various time points as specified in the Trial Flow Chart.

If, at the time of first dose of study treatment, the translated version of the FKSI-DRS,(one of the PRO measures),is not available for that language/country, and it cannot be completed by the subject at Cycle 1, Day 1, then the FKSI-DRS will not be required for this subject at any point of the study. The other study PRO measures must be completed as scheduled. Note: for some sites, the translated FKSI-DRS might become available after study startup and should be administered to subjects at their time of first dose of study treatment; for some sites the FKSI-DRS translation might not be available for the entire duration of the study. Missing FKSI-DRS for such a reason will not be considered a protocol deviation.

7.1.2.8.2 EORTC-QLQ-C30

The EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scale scoring with anchors (1=very poor and 7=excellent). This assessment will be completed at various time points as specified in the Trial Flow Chart.

7.1.2.8.3 EuroQol EQ-5D-3L

The EuroQol EQ-5D-3L is a standardized instrument for use as a measure of health outcome and will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [56]. Each dimension is rated on a three-point scale from 1 (extreme problem) to 3 (no problem).

The EuroQol EQ-5D-3L also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment.

Electronic PROs, in the order of FKSI-DRS, EORTC QLQ-C30 and EuroQol EQ-5D-3L, will be completed by the patient prior to all other study procedures and is to be completed at various time points as specified in the Trial Flow Chart.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Study Procedures Manual. Refer to Section 6.0 -- Trial Flow Chart for the timing of laboratory assessments.

7.1.3.1 Urine Pregnancy Test

For women of childbearing potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Monthly pregnancy testing should be conducted as per local regulations where applicable.

7.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 14. The schedule of individual laboratory tests is shown in the Trial Flow Chart (Section 6.0).

Table 14 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum or urine pregnancy β-human chorionic gonadotropin (β-hCG) test[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT or INR
Platelet count	ALT	Protein	
WBC	AST	Specific gravity	
Absolute Neutrophils	Bicarbonate[b]	Microscopic exam, if abnormal results are noted[c]	
Absolute Lymphocytes	Blood Urea Nitrogen[d]		
Absolute Monocytes	Calcium		
Absolute Eosinophils	Corrected Calcium[e]		
Absolute Basophils	Chloride		
	Creatinine[f]		
	Glucose		
	Lactase Dehydrogenase		
	Phosphorus or Phosphate		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Thyroid function: FT3[g], FT4, and TSH		

a. Perform on women of childbearing potential only.
b. If considered standard of care in your region.
c. Institutional standards are acceptable.
d. Urea may be used if site cannot perform Blood Urea Nitrogen
e. Corrected calcium is only needed at screening (this is used to determine IMDC criteria).
f. GFR (measured or calculated) or CrCl can be used in place of creatinine if site cannot perform creatinine.
g. Free T3 may be performed in place of Total T3 per local standards

Safety laboratory tests will be performed within 10 days prior to randomization, and post randomization according to the schedules outlined in Section 6.0 – Trial Flow Chart. Clinical chemistry and hematology results should be available prior to each dosing of pembrolizumab to determine whether pembrolizumab should be dosed.

There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function tests (FT3, FT4 and TSH) results after dosing is acceptable.

7.1.3.3 Pharmacokinetic Evaluations/Anti-pembrolizumab Antibodies

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure, samples for pre-dose trough PK and anti-drug (pembrolizumab) antibodies (ADA) samples will be collected for subjects who are randomized to the pembrolizumab plus axitinib arm as specified in Trial Flow Chart (Section 6.0).

Pre-dose trough PK and ADA samples for the pembrolizumab plus axitinib arm will be collected on Day 1 of Cycles 1, 3, 5, every 4 cycles thereafter (C9D1, C13D1, C17D1) and 30 days after discontinuation of pembrolizumab. Pre-dose trough samples should be drawn within 24 hours prior to pembrolizumab infusion.

Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at C1D1 and C9D1. If dosing of pembrolizumab is interrupted/delayed due to an AE, shift the PK samples to the next day of pembrolizumab dosing. PK post-dose sampling should occur with pembrolizumab dosing regardless of axitinib dosing status. If axitinib is interrupted/delayed at C9D1, but pembrolizumab is dosed, the post-dose PK sample should still be drawn.

Date and times of the PK pre-administration sample, start of the administration of pembrolizumab, completion of the administration of pembrolizumab, and PK post-administration samples must be recorded and entered into the eCRF.

Every effort should be taken to collect samples at 30 days after end of pembrolizumab treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical trials, it may be decided to discontinue or reduce further sample collection in this study. Pharmacokinetic data may also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis may be performed to characterize PK parameters (clearance [CL], volume of distribution [V]) and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen. Pharmacokinetic data may also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

7.1.3.4 Tumor Tissue Collection

Obtain tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. It is strongly encouraged, if possible, to obtain a fresh biopsy if the archived tumor tissue is greater than 3 years old. Informed consent for the study must be taken prior to collection of a fresh biopsy. If the subject signs the FBR consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR (see Section 7.1.3.7 for the rationale). Details regarding time points for collection of tumor tissue are outlined in the Trial Flow Chart, Sections 6.1 and 6.2.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.3.5 Blood Collections for ctDNA, TCR, RNA, Plasma and Serum Biomarker Analyses

The following samples must be collected prior to dosing time points in accordance with the Trial Flow Chart in Section 6.0: ctDNA, TCR, RNA, plasma for biomarker analyses and blood for serum biomarker analyses.

Leftover samples may be kept for future biomedical research if the subject signs the FBR consent.

Detailed instructions for sample collection, storage and shipment instructions for serum samples will be provided in the study Procedures Manual.

7.1.3.6 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual

7.1.3.7 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover archival or fresh biopsy tumor tissue
- Leftover RNA from blood
- Leftover serum and plasma from biomarker analyses

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the trial should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End of Treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who attain a CR or complete 35 trial treatments (approximately 2 years) of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or of the 35 trial treatments, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.2) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.3.3).

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Written consent for the study must be obtained prior to performing any protocol-specific procedure including the mandatory newly obtained (fresh) tumor biopsy that is required for eligibility (in the event an archival sample is not available). Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 – Entry Criteria. Visit requirements are outlined in Section 6.0 -Trial Flow Chart.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days prior to randomization with these additional required time frames:

- Safety assessments including clinical laboratory tests, ECG, vital signs, and evaluation of KPS are to be performed within 10 days prior to randomization.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If the randomization pregnancy test is more than 72 hours prior to the first dose of study treatment, it should be repeated. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Screening procedures may be repeated after consultation with the Sponsor. Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria after consultation with the Sponsor. Assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

7.1.5.2.1 Second Course Phase (Retreatment Period)

Section 5.8.3 describes eligibility for second course of pembrolizumab treatment. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.1.5.3 Post-Treatment

7.1.5.3.1 End of Treatment

The End of Treatment Visit should occur at the time study treatment is discontinued for any reason. If the End of Treatment Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the End of Treatment visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 6.0- Trial Flow Chart. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8– Subject Withdrawal/Discontinuation Criteria.

Subjects who discontinue trial treatment for reasons other than disease progression will **still be considered on study** and should continue with regularly scheduled assessments listed in the Imaging Follow-up Visit on the Trial Flow Chart (Section 6.0; also refer to Section 7.1.5.3.3).

7.1.5.3.2 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days (± 3 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment if this occurs prior to 30 days after the last dose of study treatments.

Subjects who are eligible for re-treatment with pembrolizumab (as described in Section 5.8.3) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.3.3 Imaging Follow-up Visits

Subjects who discontinue treatment for reasons other than BICR verified PD should continue with imaging assessments per the protocol defined schedule until: 1) PD is BICR verified, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion or early termination, whichever occurs first.

Subjects who are eligible to receive second course retreatment with pembrolizumab according to the criteria in Section 5.8.3 will have imaging assessments and schedules per those set for Second Course of treatment as described in Section 6.0 – Trial Flow Chart.

7.1.5.3.4 Survival Follow-up Visits

Subjects who experience PD that is verified by BICR or further confirmed by the investigator or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose exceeding 5 times the prescribed dose of pembrolizumab (200 mg), defined as any dose higher than 1000 mg. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. Overdose for sunitinib and axitinib is any dose exceeding the prescribed maximum dose for each drug (i.e., 5 mg BID for axitinib unless dose escalation to 7 mg or 10 mg BID is permitted per Section 5.2.1.2.1. or 50 mg QD for sunitinib). There is no specific treatment for sunitinib or axitinib overdose. In the event of overdose, the dose should be interrupted and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. The subject may resume study treatment at the discretion of the investigator (refer to axitinib and sunitinib labeling for more details).

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 15 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. The following events should also be reported as an ECI if they occur after the start of treatment in the axitinib/ pembrolizumab combination arm:

   a. events with ALT and/or AST > 5xULN

   b. events with ALT and/or AST > 3xULN concurrently with total bilirubin ≥2xULN

7.2.3.3 Protocol-specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The eDMC will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 15 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

7.3.3 Data Monitoring Committee

An external Data Monitoring Committee (eDMC) will be formed prior to study start to periodically monitor safety and evaluate the interim data from this trial. The members of the committee are external to the Sponsor, are not involved with the trial in any other way (e.g., they cannot be trial investigators) and have no competing interests that could affect their roles with respect to the trial.

The eDMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the eDMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the eDMC charter that is reviewed and approved by all the eDMC members.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans may be developed for PK/modeling analysis,

biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.12.

Study Design Overview	This is a randomized, open-label, multicenter Phase III trial to evaluate efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or mRCC.
Treatment Assignment	Approximately 840 subjects will be randomized 1:1 into the following two treatment arms: Arm 1 will receive the combination therapy of pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W) and axitinib 5 mg twice daily (BID) taken orally; Arm 2 will receive sunitinib monotherapy 50 mg daily (QD) taken orally for 4 weeks then off treatment for 2 weeks. Stratification factors are provided in Section 5.4. This is an open-label study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. Progression-free survival (PFS), per RECIST 1.1 by BICR review 2. Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary hypotheses for PFS and OS will be evaluated by comparing pembrolizumab in combination with axitinib to sunitinib using a stratified log-rank test. Estimation of the hazard ratio will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. Stratified Miettinen and Nurminen's method with weights proportional to the stratum size will be used for comparison of the objective response rates (ORR) between the treatment arms.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this trial. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% confidence intervals for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.

Interim and Final Analyses	Two interim analyses are planned for the study. Results will be reviewed by an external data monitoring committee (eDMC). Details are provided in Section 8.7. • First Interim Analysis (IA1) o Timing: To be performed after enrollment completion, once a 7-month minimum follow up (ie, 7 months since last subject is randomized) has been achieved and a minimum of 305 PFS events have accrued. It is expected to be 22 months after the first subject randomized (study start). Approximately 48% of the final required OS events (or 195 deaths) are expected at that time. o Purpose: First interim analysis for PFS and OS. • Second Interim Analysis (IA2) o Timing: To be performed when approximately 74% of the final required OS events (or 299 deaths) have accrued, expected to be 31 months after study start. At IA2, approximately 487 PFS events are expected. o Purpose: Final analysis for PFS and IA2 for OS. • Final analysis (event-driven trial) o Timing: When approximately 404 deaths have accrued, expected to be 43 months after study start. o Purpose: Final analysis for OS (assuming not declared successful at the interim analysis)
Multiplicity	The overall Type I error rate is strongly controlled at 2.5% (1-sided) with 0.2% initially allocated to PFS and 2.3% initially allocated to OS. A group sequential approach will be used to allocate alpha between the interim and final analyses. The study will be considered a success if either PFS or OS is demonstrated to be statistically significant under multiplicity control. Note that the study would continue for OS even if PFS is shown to be statistically significant at IA1 or IA2.
Sample Size and Power	The sample size was planned for 840 but the following power calculations are based on the actual final number of randomized subjects (N = 861). There are 2 primary endpoints for this study, PFS, and OS. The expected median PFS time in the control group is 13 months. Based on 487 PFS events, the study has ~99% power to detect a hazard ratio of 0.60 for PFS (pembrolizumab+axitinib combination vs. sunitinib) at alpha=0.2% (1-sided). The expected median OS time in the control group is 33 months. Based on 404 death events, the study has 80% power to detect a hazard ratio of 0.75 for OS at alpha=2.3% (1-sided).

8.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

Although the trial is open label, analyses or summaries generated by randomized treatment assignment and/or actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. In addition, independent central imaging review will be performed without knowledge of the treatment group assignments of the subjects.

The eDMC will serve as the primary reviewer of the unblinded results of the PFS and OS at interim analyses and may make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendations of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to evaluate and direct the Sponsor protocol team as to the appropriate actions to be taken on these recommendations. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

8.4.1.1 Primary

Progression-free Survival (PFS) – RECIST 1.1 by Blinded Central Imaging Vendor Review

Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 8.6.1 for the censoring rules.

Overall Survival (OS)

Overall survival is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow up.

8.4.1.2 Secondary

Objective Response Rate (ORR) – RECIST 1.1 by BICR

Objective response rate is defined as the proportion of the subjects in the analysis population who have a CR or PR per RECIST 1.1.

Duration of Response (DOR) - RECIST 1.1 by BICR

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. See Section 8.6.1 for the censoring rules.

Disease Control Rate (DCR) - RECIST 1.1 by BICR

Disease control rate is defined as the percentage of subjects who have achieved CR, PR, or SD of ≥ 6 months based on assessments by BICR per RECIST 1.1.

8.4.2 Safety Endpoints

Safety endpoints are described in Sections 4.2.3.2.

8.5 Analysis Population

8.5.1 Efficacy Analysis Population

The Intention-to-Treat (ITT) population will serve as the population for the primary efficacy analyses. All randomized subjects will be included in this population. Subjects will be analyzed in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.6.1 – Statistical Methods for Efficacy Analyses.

The analysis population of DOR consists of responders.

8.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be analyzed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

8.6.1.1 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group including the PFS rates at 12, 18, and 24 months (based on data adequacy). The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR. Death is always considered as a confirmed PD event. Subjects who do not experience a PFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment and PFS with PD determined per irRECIST by BICR, as indicated in the exploratory objectives.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, one primary and two sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if PD or death events occur immediately after more than one missing disease assessment, the PFS data are censored at the last disease assessment prior to the missing visits. Also, data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy.

The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than complete response or initiation of new anti-cancer treatment (whichever occurs later) to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 16.

Table 16 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

PD = progressive disease; PFS = progression-free survival.

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function vs. time for PFS will be plotted for the comparison between pembrolizumab+axitinib combination and the control arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies. Further details of sensitivity analyses will be described in the SAP.

8.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves in each treatment group including the OS rates at 12, 18, and 24 months (based on data adequacy). The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

8.6.1.3 Objective Response Rate

Stratified Miettinen and Nurminen's method with weights proportional to the stratum size will be used for comparison of the objective response rates between the treatment arms. A 95% CI for the difference in response rates between the treatment arms will be provided. The stratification factors used for randomization will be applied to the analysis. Sensitivity analyses will be performed to assess ORR based on investigator's assessment.

The ORR analysis will be conducted according to the hypothesis testing plan as described in Section 8.7 – Interim Analyses and Section 8.8 – Multiplicity.

8.6.1.4 Duration of Response

The non-parametric Kaplan-Meier method will be used to estimate the DOR curve in each treatment group; estimates of the percentage of subjects still in response and 95% CIs at specific duration time points will be provided.

Sensitivity analyses will be performed to assess DOR based on investigator's assessment.

For each DOR analysis, a corresponding summary of the reasons responding subjects are censored will also be provided.

Censoring rules for DOR are summarized in Table 17.

Table 17 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (Non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (Non-event)
Death or progression immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥ 2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (Non-event)
Death or progression after ≤ 1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (Event)

A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.
Abbreviations: DOR=duration of response; PD=progressive disease.

8.6.1.5 Disease Control Rate

Stratified Miettinen and Nurminen's method with weights proportional to the stratum size will be used for comparison of the DCR between the treatment arms. A 95% CI for the difference in response rates between the treatment arms will be provided. The stratification factors used for randomization will be applied to the analysis. Sensitivity analyses will be performed to assess DCR based on investigator's assessment.

8.6.1.6 Summary of Statistical Methods for Efficacy

Table 18 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 8.7 Interim Analyses and in Section 8.8 Multiplicity.

Table 18 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data/ Censoring Approach
Primary Hypothesis #1			
PFS per RECIST 1.1 by BICR	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
Primary Hypothesis #2			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last date the subject was known to be alive
Secondary Hypothesis			
ORR per RECIST 1.1 by BICR	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 5.4) will be applied to the analysis model.
‡ Miettinen and Nurminen method.
Abbreviations: BICR=blinded independent central imaging review; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 19). The tiers differ with respect to the analyses that will be performed. For this protocol, there are no Tier 1 events.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 10% of the subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 10% of subjects with events was chosen for Tier 2 event because the incidence rate would allow meaningful statistical assessments; events reported in less frequent than 10% of subjects would obscure the assessment of overall safety profile and add little to the meaningful interpretation. Because many 95% CIs may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and predefined limits of change.

Continuous measures such as changes from baseline in laboratory values and vital signs that are not pre-specified as Tier 1 safety parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with Grade 3-5 AE (incidence ≥5% of subjects in one of the treatment groups) and any SAE (incidence ≥5% of subjects in one of the treatment groups) will be considered Tier 2 endpoints.

The threshold of at least 5% of subjects with events was chosen for Tier 2 Grade 3-5 AEs and SAEs because the incidence rate would allow meaningful statistical assessments; those AEs are expected to happen less frequent than specific AEs/SOCs but important for overall safety profile assessment.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any Grade 3-5 AE (incidence <5% of subjects in one of the treatment groups), any SAE (incidence <5% of subjects in one of the treatment groups), any drug-related AE, any AE that is both drug-related and Grade 3-5, any AE that is both serious and drug related, dose modification due to AE, discontinuation due to an AE, and death will be considered Tier 3 endpoints.

Note that 95% CIs will be provided for between- treatment differences in the percentage of subjects with Tier 2 events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Table 19 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any Serious AE (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Any Grade 3-5 AE (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific AEs or SOCs (incidence ≥10% of subjects in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Serious AE (incidence <5% of subjects in one of the treatment groups)		X
	Any Grade 3-5 AE (incidence <5% of subjects in one of the treatment groups)		X
	Any Serious and Drug-related AE		X
	Any Grade 3-5 and Drug-related AE		X
	Dose Modification due to AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs or SOCs (incidence <10% of subjects in all of the treatment groups) or PDLCs		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

Abbreviations: AE = adverse event; CI = confidence interval; ECG = electrocardiogram; PDLC = pre-defined limit of change; SOC = system organ class.

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (e.g., age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

There are 2 planned interim analyses for OS and 1 planned interim analysis for PFS in this trial. Results of the interim analyses will be reviewed by an eDMC. Table 20 shows analysis strategies for each interim and final analysis in this trial based on model assumptions. Table 20 will be updated using the actual number of events at the interim and final analyses and the same spending function used to derive the design in this table. All futility boundaries are non-binding in this study.

Table 20 Summary of Interim and Final Analyses Strategies

Analysis	Expected Months after Study Start	Hypothesis Tested in the Analysis	True Hazard Ratio	n[+]	Information Fraction	Type I Error (Overall α)	Efficacy Boundary Crossing				Futility Boundary Crossing			
							Nominal α	Z-value	Statistics[‡]	Power[§]	Nominal α	Z-value	Hazard Ratio	Cumulative Type II Error
IA1	22 Months	PFS	0.6	365	0.75	0.20%	0.11%	3.06	0.73	~96.5%	22.1%	-0.77	1.08	<0.01%
						1.35%	0.74%	2.44	0.77	~99.2%	21.8%	-0.78	1.08	<0.01%
						2.5%	1.36%	2.21	0.79	~99.6%	21.6%	-0.79	1.08	<0.01%
		OS	0.75	195	0.48	2.3%	0.01%	3.72	0.59	~4.3%	4.1%	-1.74	1.28	~0.01%
						2.5%	0.01%	3.70	0.59	~4.5%	4.1%	-1.74	1.28	~0.01%
		ORR	-	860	1.0	0.2%	0.2%	2.88	9.4%	>99.9%	-	-	-	-
						1.15%	1.15%	2.27	7.4%	>99.9%				
						2.5%	2.5%	1.96	6.4%	>99.9%				
IA2	31 Months	PFS	0.6	487	1.0	0.2%	0.14%	3.00	0.76	>99.9%	99.8%	3.00	0.76	~3.9%
						1.35%	1.02%	2.32	0.81	>99.9%	98.7%	2.32	0.81	~0.04%
						2.5%	1.95%	2.06	0.83	>99.9%	97.5%	2.06	0.83	~0.02%
		OS	0.75	299	0.74	2.3%	0.78%	2.42	0.76	~52.7%	20.3%	-0.84	1.10	~0.05%
						2.5%	0.92%	2.36	0.76	~55.1%	20.2%	-0.85	1.10	~0.05%
FA	43 Months	OS	0.75	404	1.0	2.3%	2.07%	2.04	0.82	~80.8%	97.7%	2.04	~0.82	~19.2%
						2.5%	2.22%	2.01	0.82	~81.7%	97.5%	2.01	~0.82	~18.3%

[+] n means expected events at the time of corresponding analysis for PFS and OS based on model assumption. In the rare case if PFS events accumulate slower than expected, a minimum of 305 events is required at 22 months to trigger IA1; n means total sample size for ORR.

[‡] The statistics used here are hazard ratio for PFS and OS, and ORR Δ for ORR where ORR Δ = ORR in (pembrolizumab+axitinib group) – ORR in sunitinib group.

[§] The power calculated for OS is cumulative power. For the power calculation, the target ORR in the pembrolizuab+axitinib group and the reference ORR assumed in the sunitinib groups are 55% and 31%, respectively.

For OS, a linear spending function with a fixed alpha spending of 0.0001 at IA1 and the rest alpha spending approximated by a Hwang-Shih-DeCani (HSD) alpha-spending function with gamma parameter (-4) is used to construct Haybittle-Peto type of group sequential boundaries to control the overall Type I error rate for this endpoint at 2.3% or 2.5% (1-sided). Futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with gamma parameter (-6) is used to construct group sequential boundaries for futility. The Type I error rate to spend at IA2 and FA will be determined by the spending function evaluated at the exact number of deaths at each analysis.

For PFS, an HSD alpha-spending function with gamma parameter (-2), is used to construct group sequential boundaries to control the overall Type I error rate for this endpoint at 0.2%, 1.35% and 2.5% (1-sided). Futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with gamma parameter (-6) is used to construct group sequential boundaries for futility. The Type I error rate to spend at the interim analysis will be determined by the spending function evaluated at the exact number of PFS events at each analysis.

For ORR, if the testing of ORR hypothesis does not reach statistical significance at interim analysis 1 (IA1), the p-value from the IA1 analysis can be compared to an updated α-level if the null hypothesis for PFS or OS is rejected at a later time.

The purpose of the first interim analysis is to conduct the interim testing for efficacy on both PFS and OS endpoints. It will be performed after enrollment completion, which is expected after 15 months since start of the study. The IA1 data cutoff is to occur once a minimum of 305 PFS events have accrued and all patients have been followed up for at least 7 month after randomization. A minimum of 305 PFS events will ensure at least 90% power for the PFS analysis at IA1. The minimum follow-up time requirement is to ensure sufficient follow up for the PFS endpoint to characterize the PFS curves at the tail and ensure sufficient follow up for the ORR endpoint for this interim analysis. Based on fulfilling these two criteria for IA1, IA1 is projected to happen at approximately 22 months after the start of the study with approximately 365 PFS events based on model assumptions (see Table 20). In the unexpected case that there are fewer than 305 PFS events when all subjects have had the opportunity to be followed up for at least 7 months after randomization, the interim analysis will be delayed until 305 PFS events have accrued.

The second interim analysis is to conduct the final analysis for the PFS endpoint if the superiority of PFS has not been demonstrated in the first interim analysis and to conduct the second interim testing of the OS endpoint. It will be performed when approximately 74% of the final required OS events (or 299 deaths) have accrued, expected after 31 months from the start of the study. It is expected to accumulate 487 PFS events at that time.

The final analysis for the study will be conducted when the target number of OS events (404 deaths) is reached, projected to occur at 43 months after the start of the study, if the study has not been stopped early for efficacy.

In the first interim analysis, if the study demonstrates superiority of PFS but has not demonstrated superiority of OS (without crossing the futility boundary for OS), the study will continue for OS after the interim analysis.

If superiority of pembrolizumab in combination with axitinib relative to sunitinib with respect to PFS or OS is demonstrated, the ORR hypothesis will be tested using the p-value from the first interim analysis with the overall Type I error $\alpha = 0.2\%$, 1.15%, or 2.5%, depending on the results of the OS and PFS hypothesis tests. Since all subjects will have an opportunity to have at least 4 scheduled scans at the time of the first interim analysis if not discontinued prior to the first interim analysis data cut-off, they all will be included in this ORR analysis.

The DMC has responsibility for assessment of overall risk: benefit. The DMC will review safety periodically (every 4 months in the first year and frequency may be reduced after one year if no unexpected safety signals occur). To account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for OS will be pre-specified in the sSAP. This analysis will be performed if requested by the DMC. However, DMC review of OS data beyond the planned efficacy analysis to assess the overall risk:benefit to trial participants will not require multiplicity assessment typically associated with a planned efficacy interim analysis because these analyses are not to declare a positive efficacy finding. Any DMC recommendation will be communicated to the Sponsor as agreed to in the DMC charter. A detailed description of the multiplicity adjustment and hypotheses testing plan is provided in Section 8.8 Multiplicity.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the 2 primary hypotheses (superiority of the pembrolizumab+axitinib combination relative to sunitinib on PFS or OS) and the secondary hypothesis of superiority of pembrolizumab+axitinib combination relative to sunitinib in ORR. Note that the study will be a success if either PFS or OS is demonstrated to be statistically significant under multiplicity control.

The overall Type I error across the testing of the OS, PFS, and ORR hypotheses is strongly controlled at α=2.5% (1-sided). The multiplicity strategy will follow the graphical approach of Maurer and Bretz. Figure 5 provides the multiplicity strategy diagram of the study.

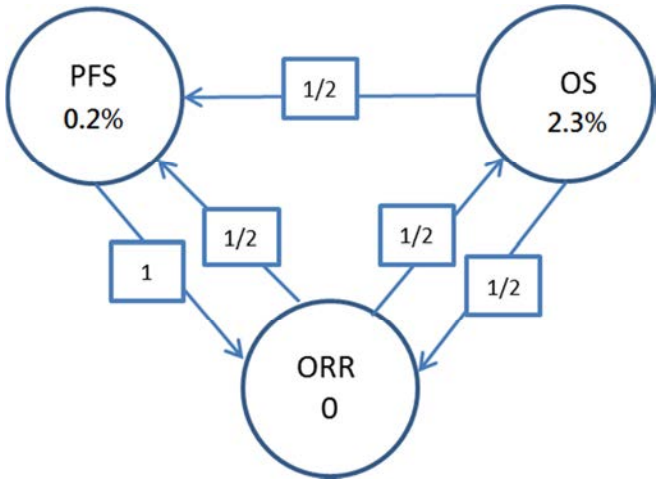


Figure 5 Multiplicity Strategy

The alpha level indicated for each null hypothesis is the alpha level initially allocated. When a particular null hypothesis is rejected, the arrows leading to it are removed and the alpha allocated to the null hypothesis will be re-distributed among all arrows going out and re-weighted per the number on the arrow (summing to 1). The arrows on the diagram show how the Type I error allocated to a hypothesis that was successfully tested will be re-distributed for the testing of the other two hypotheses. Initially, α=2.3% (23/25 of the overall total α=2.5% for testing the OS, PFS and ORR) is allocated to the OS hypothesis and α=0.2% (2/25 of the overall total α=2.5%) is allocated to the PFS hypothesis.

The testing of the OS, PFS, and ORR will proceed as follows.

PFS Hypothesis: The study allocates α=0.2%, one-sided, to test PFS hypothesis initially. If the null hypothesis for OS is rejected, Figure 5 shows that half of its α=2.3% will be reallocated to PFS hypothesis testing (α=1.35%). If null hypotheses for OS and ORR are both rejected, all α will be reallocated to test PFS hypothesis (α=2.5%). Thus, the PFS null hypothesis may be tested at α=0.2%, 1.35% or 2.5%. Table 20 shows the boundary thresholds corresponding to a successful group sequential testing of the PFS hypothesis at each of these Type I error levels. For PFS, the information fraction at interim analysis will be based on the final planned number of 487 events. A Hwang-Shih-DeCani (HSD) spending function with $\gamma = -2$ (α-spending for efficacy) is used to set efficacy bounds. The futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-

α=97.5%); an HSD alpha-spending function with γ=-6 is used to construct group sequential boundaries for futility. The boundary thresholds at the interim analysis will be determined by the spending function evaluated at the exact number of PFS events at each analysis. Note that if the α-reallocation from OS hypothesis testing occurs at the final analysis after hypothesis testing for PFS has been completed, the previously computed PFS test statistic for the PFS analysis may be re-evaluated versus the updated bounds.

OS Hypothesis: The OS hypothesis may be tested at α=2.3% (initially allocated α) or at α=2.5% (if both the ORR and PFS null hypotheses are rejected). The nominal Type I error rates for the interim analysis and final analysis that will allow tight control of the overall Type I error for testing the OS hypothesis will be derived using the alpha-spending function approach based on the overall Type I error allocated to the OS hypothesis. The group sequential testing of the OS hypothesis will use a linear α-spending function with a fixed α-spending of 0.0001 at IA1 and the rest α-spending approximated by an HSD α-spending function with γ=-4 to construct Haybittle-Peto type of group sequential boundaries to control the overall Type I error rate for this endpoint at 2.3% or 2.5% (1-sided). The futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with γ=-6 is used to construct group sequential boundaries for futility. The boundary thresholds will be updated using the actual number of OS events at the interim and final OS analyses and the same spending function used to derive the design.

ORR Hypothesis: The ORR hypothesis will be tested with all subjects, since all subjects will have "mature ORR information," with an opportunity to complete 4 scheduled scans at the first interim analysis. The ORR hypothesis is initially allocated a Type I error α=0% and thus, cannot be tested unless one or both of the PFS or OS null hypotheses have been rejected. Depending on the results of the OS and PFS hypotheses testing, the ORR hypothesis can be tested at an overall Type I error levels of α=0.2%, 1.15%, or 2.5%. If the testing of ORR hypothesis does not reach statistical significance at interim analysis 1 (IA1), the p-value from the IA1 analysis can be compared to an updated α-level if the null hypothesis for PFS or OS is rejected at a later time. Table 20 shows the boundary thresholds of the ORR hypothesis at each of these Type I error levels.

8.9 Sample Size and Power Calculations

The study will randomize subjects in a 1:1 ratio into the experimental arm of pembrolizumab+axitinib and the control arm of sunitinib. Both PFS and OS are primary endpoints for this study. The sample size was planned for 840 but the following power calculations are based on the actual final number of randomized subjects (N = 861).

For the PFS endpoint, based on a target number of 487 PFS events and one interim analysis at approximately 75% of the target number of events, the study has ~99% power to detect an HR of 0.60 (pembrolizumab+axitinib combination versus sunitinib) at alpha=0.2% (1-sided). The calculation assumes an HSD α-spending function with γ=-2 to control the overall Type I error rate for this endpoint at 0.2% (1-sided). The target numbers of PFS events for the first interim and final analysis are projected to occur at 22 and 31 months respectively.

For the OS endpoint, based on a target number of 404 final OS events and 2 interim analyses (with approximately 48% of final OS events at IA1 and 74% of the final OS events at IA2), the

study has approximately 80% power to detect an HR of 0.75 at an overall alpha level of 2.3% (1-sided). The calculation assumes that a linear α-spending function with a fixed α-spending of 0.0001 at IA1 and the rest α-spending approximated by an HSD α-spending function with γ=-4 to control the overall Type I error rate for this endpoint at 2.3% (1-sided). The target number of OS events is projected to occur at 43 months after the start of the study. The target numbers of OS events for the first and second interim analyses are projected to occur at 22 months and 31 months respectively.

The above calculations assume an exponential distribution with a median of 13 months for PFS and a median of 33 months for OS for the control group respectively, a yearly dropout rate of 10% for PFS and 1% for OS, and an enrollment of 15 months, with monthly accrual of 40 to 60 patients in the first 3 months and monthly accrual of ~60 patients after the first 3 months. The median PFS and median OS assumptions in the control group are based on emerging data of sunitinib from the CheckMate 214 study (59).

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the dual primary endpoints will be estimated and plotted within each category of the following classification variables:

- IMDC_risk category (favorable versus intermediate versus poor; favorable versus intermediate plus poor)
- Geographic region (North America versus Western Europe versus Rest of the World)
- PD-L1 status (combined positive score [CPS] <1 versus CPS ≥ 1)
- Age (< 65 versus ≥ 65)
- Sex (male versus female)
- Race (white versus non-white)

Country-specific populations may also be analyzed per local regulatory requirements.

For tumor tissue PD-L1 expression status, a CPS cutpoint of 1 has been established based on data from a separate study, Keynote 427 Cohort A, in subjects with advanced/metastatic clear cell RCC treated with pembrolizumab monotherapy. Details regarding establishment of the PD-L1 CPS cutpoint will be summarized in a separate document.

8.11 Compliance

Drug accountability data for trial treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Summary statistics will be provided on Extent of Exposure for the ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 21.

Table 21 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 25 mg/mL (100 mg/4 mL)	Solution for injection	Provided centrally by the Sponsor.
Axitinib 1 mg	Tablet	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Axitinib 5 mg	Tablet	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Sunitinib malate (equivalent to sunitinib 12.5 mg)	Capsule	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Sunitinib malate (equivalent to sunitinib 25mg)	Capsule	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Pembrolizumab (MK-3475) will be supplied in open-label kits containing 2 vials each. Axitinib and sunitinib will be supplied in open-label bottles.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must

designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the

authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.7 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will

not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. [insert: 'No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).' **OR** 'Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.' **OR** 'Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.' **OR** 'Saliva specimens will be collected with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.']

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

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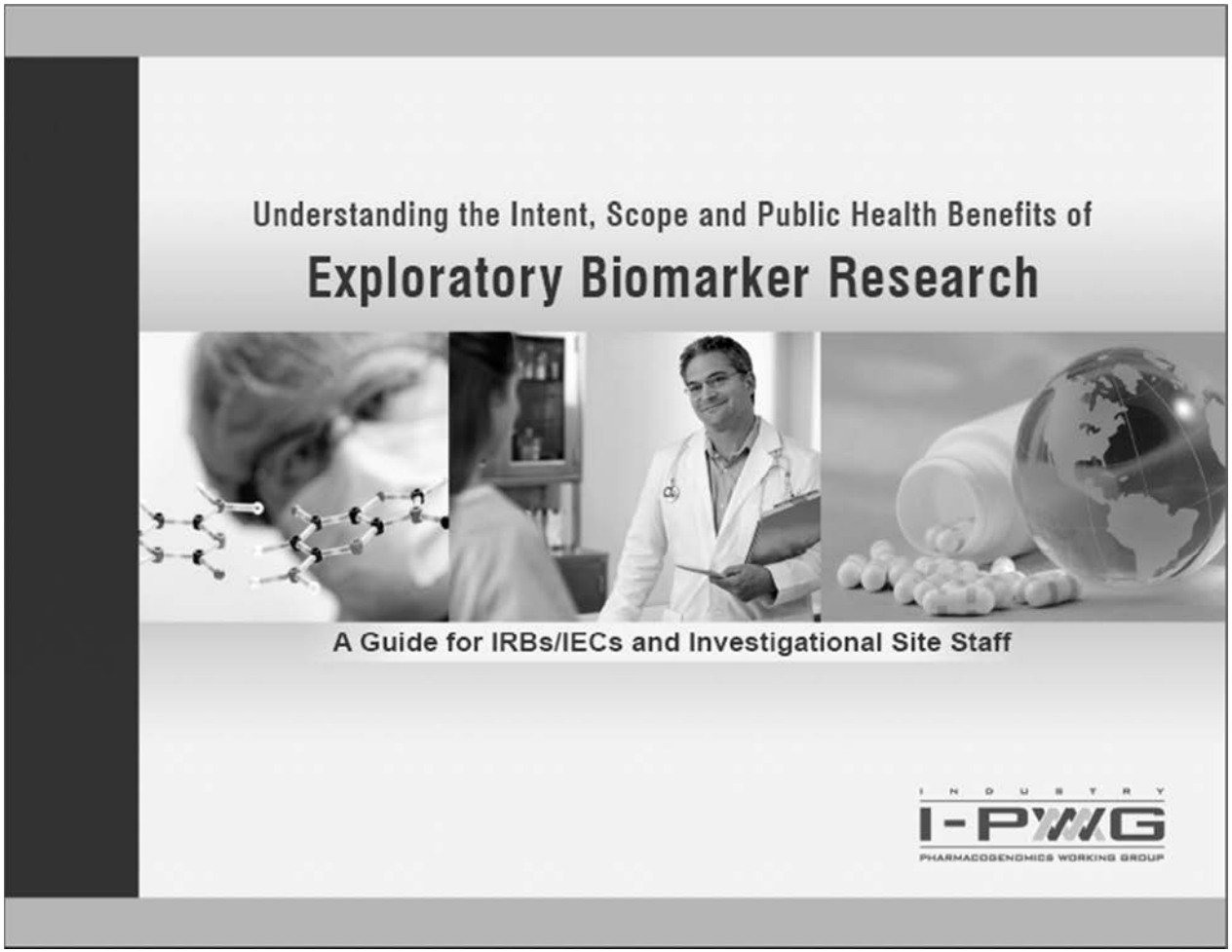
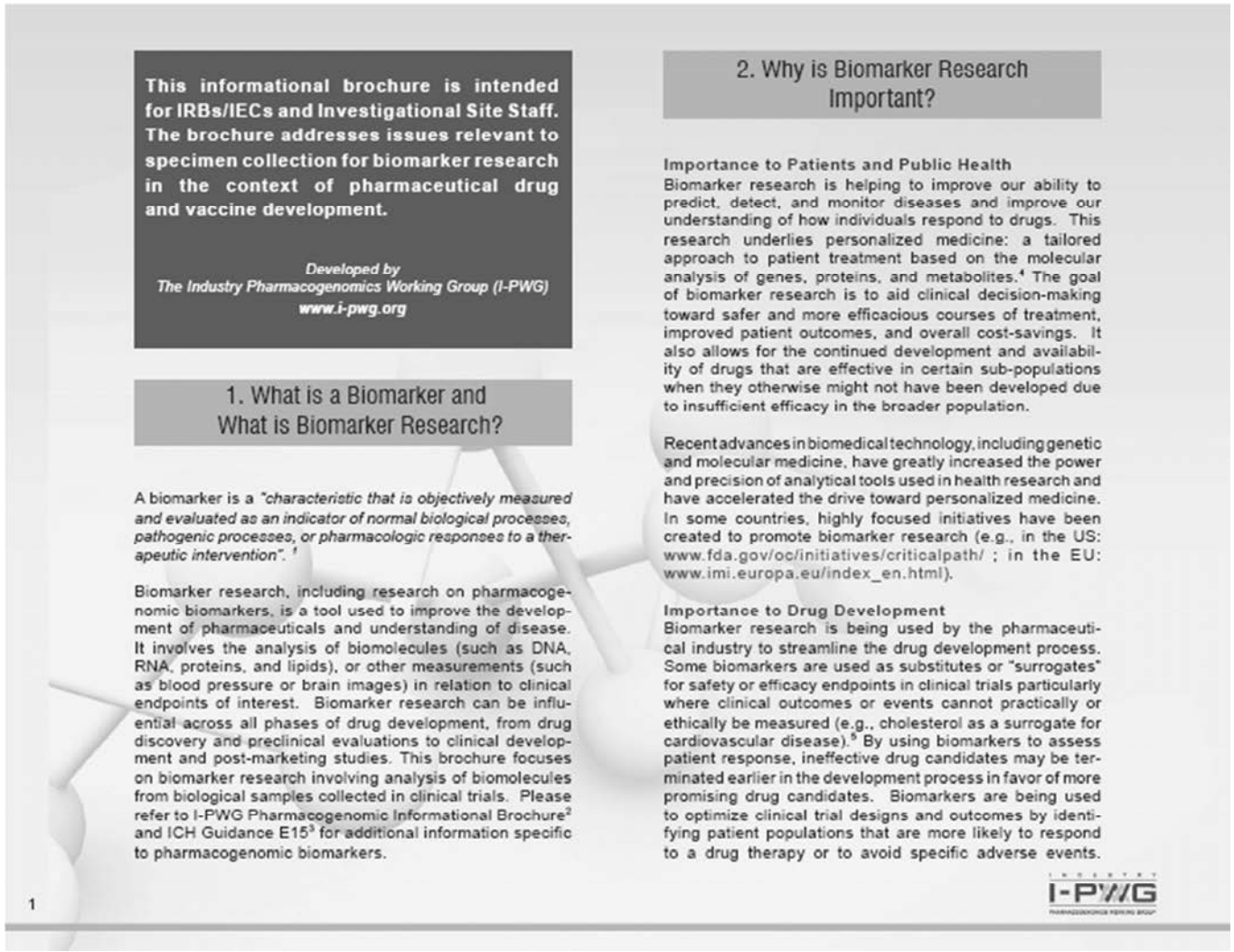
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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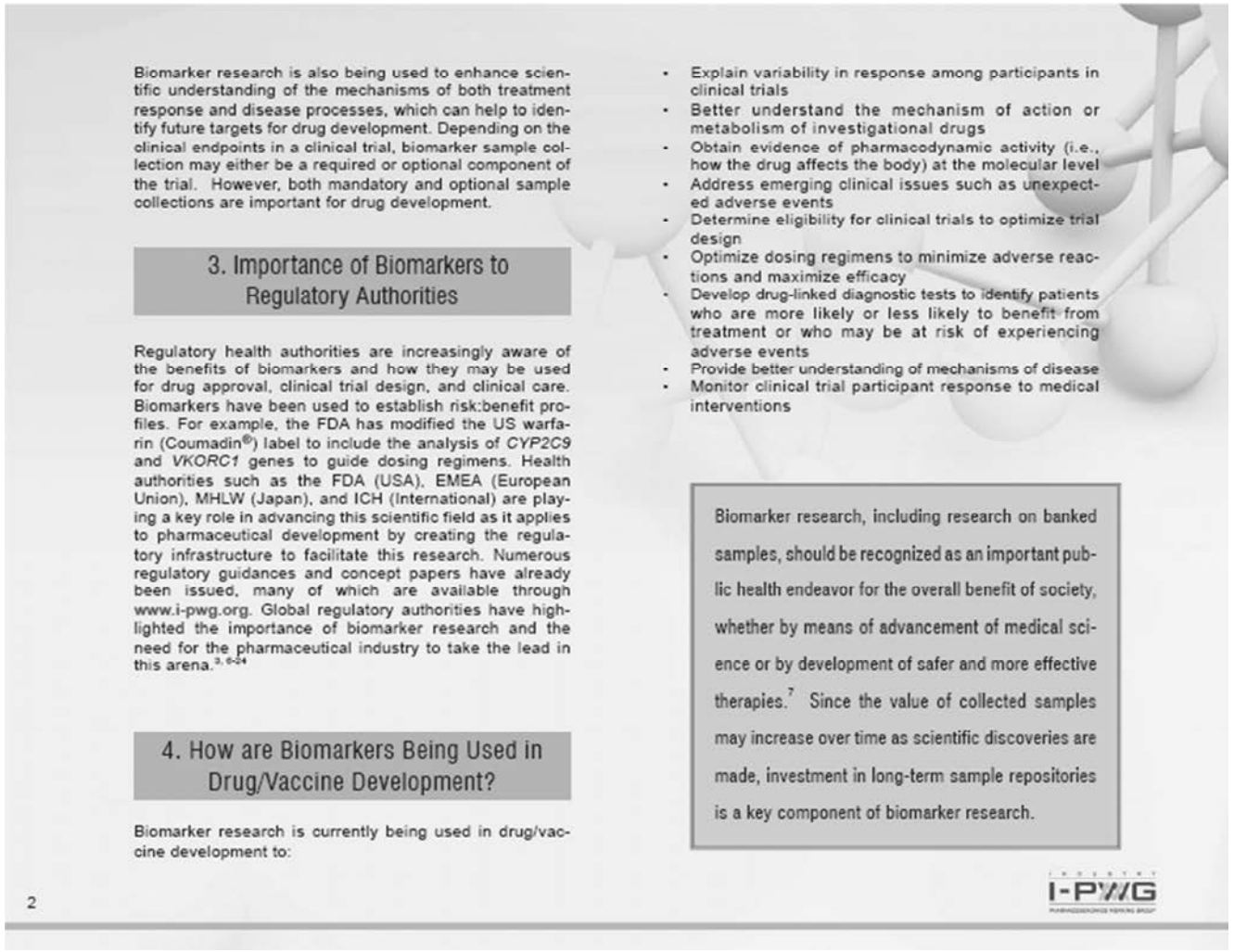

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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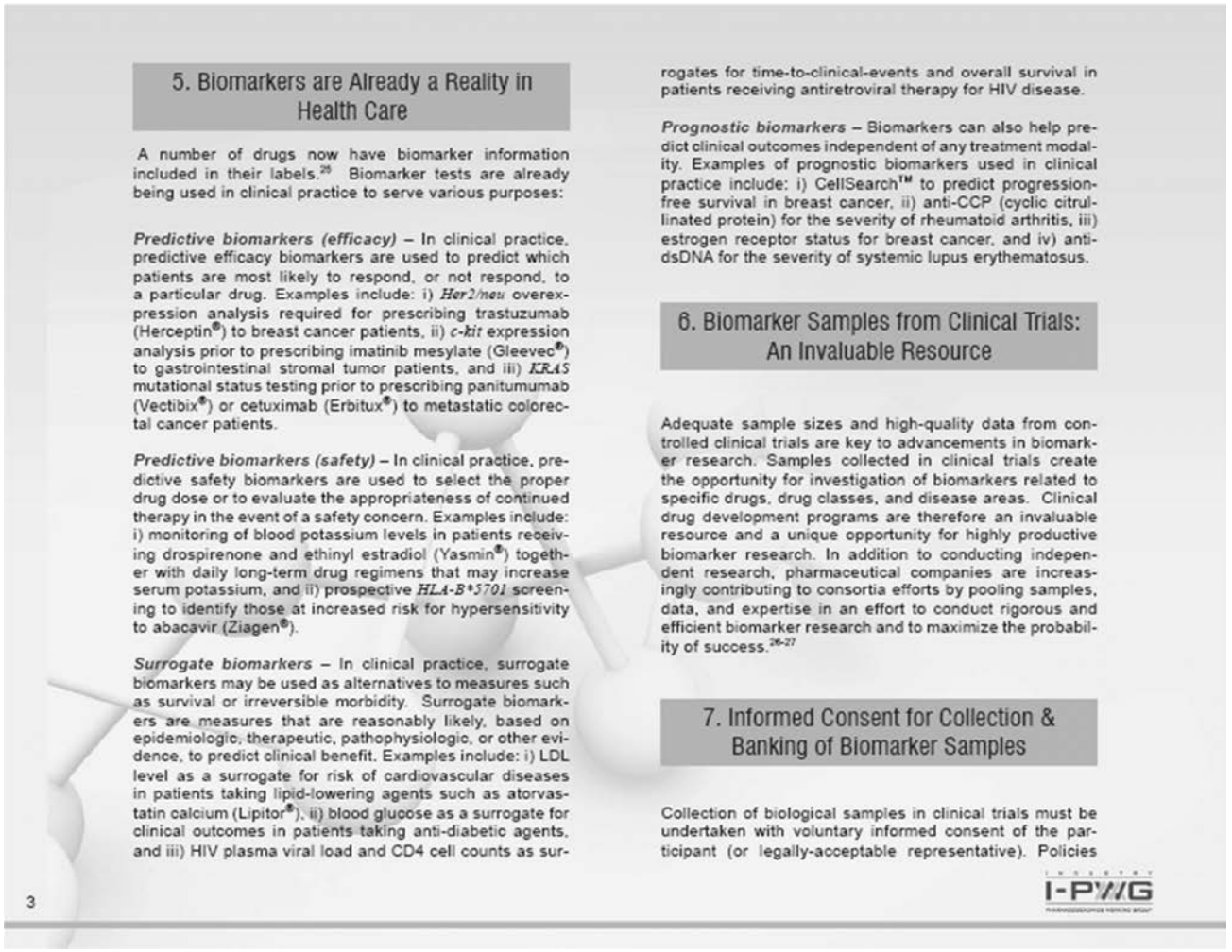

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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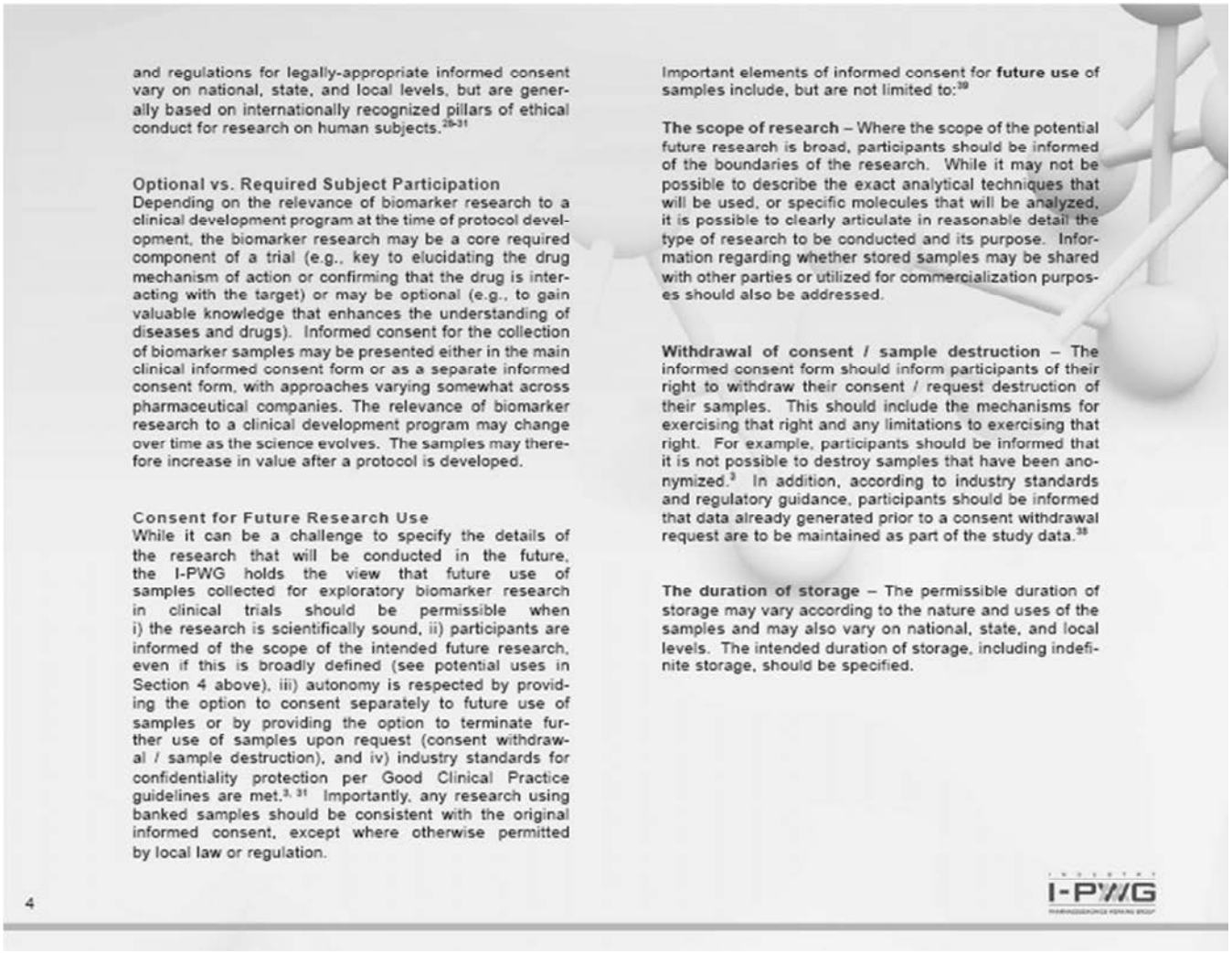

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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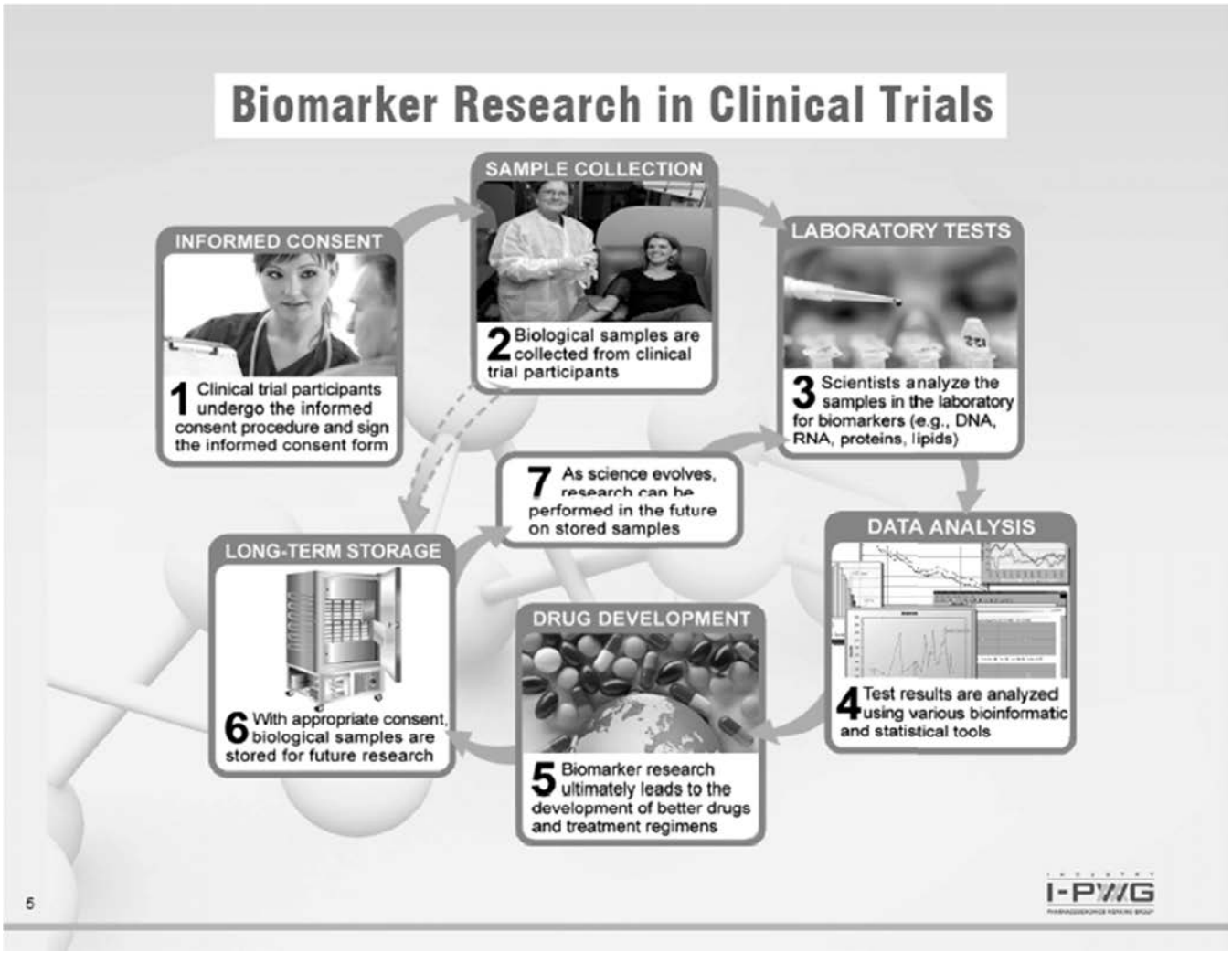
Biomarker Research in Clinical Trials
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
7 As science evolves, research can be performed in the future on stored samples
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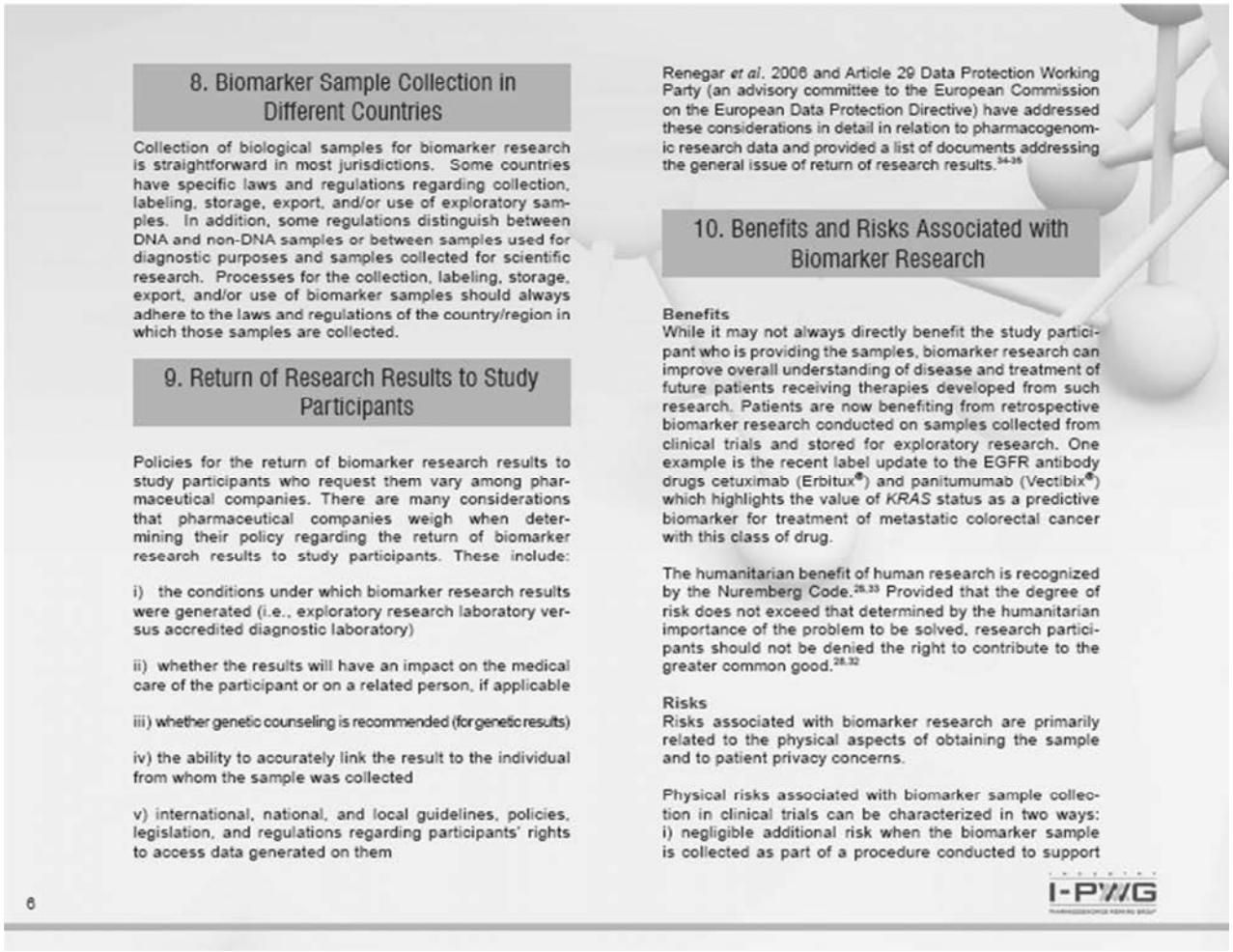

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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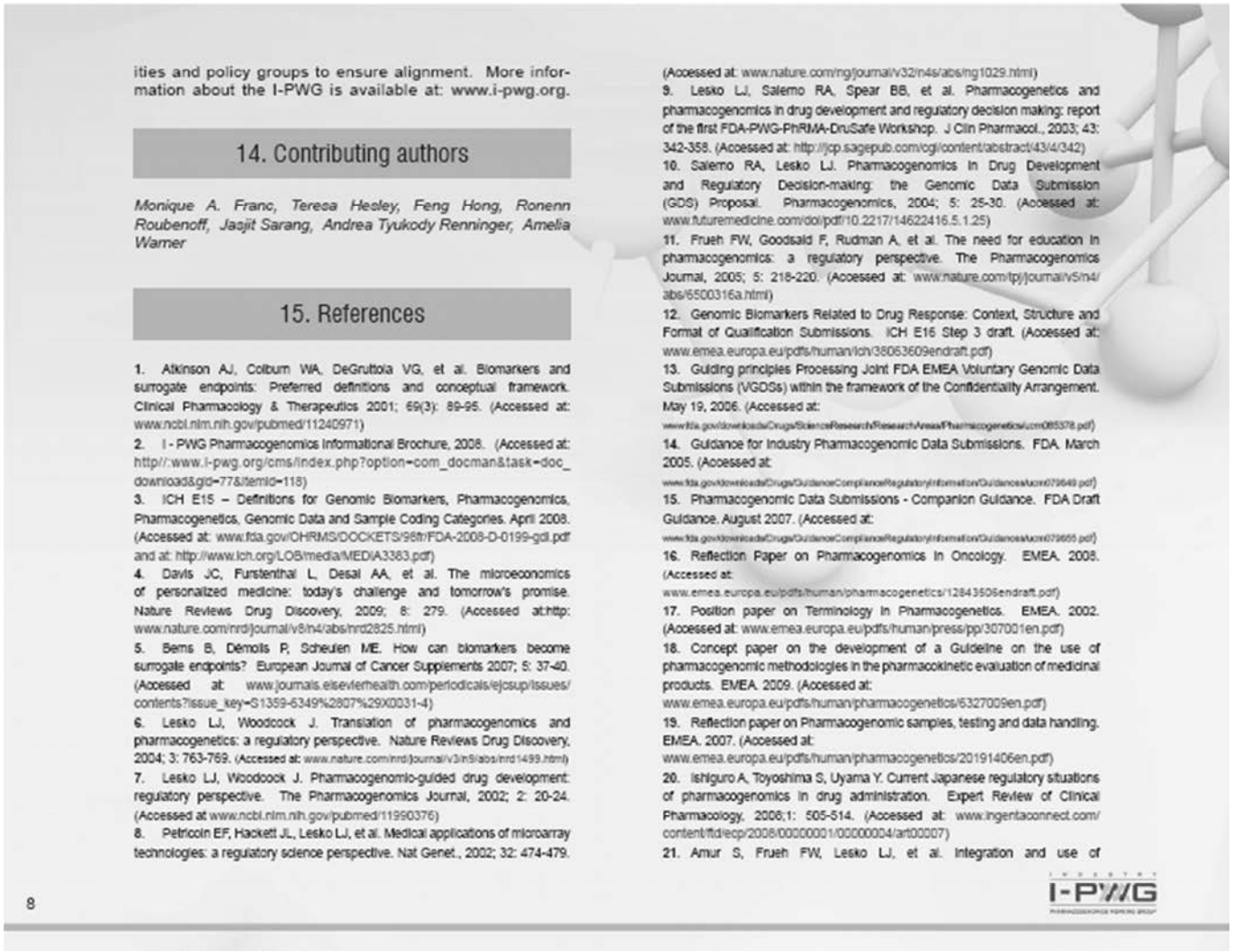

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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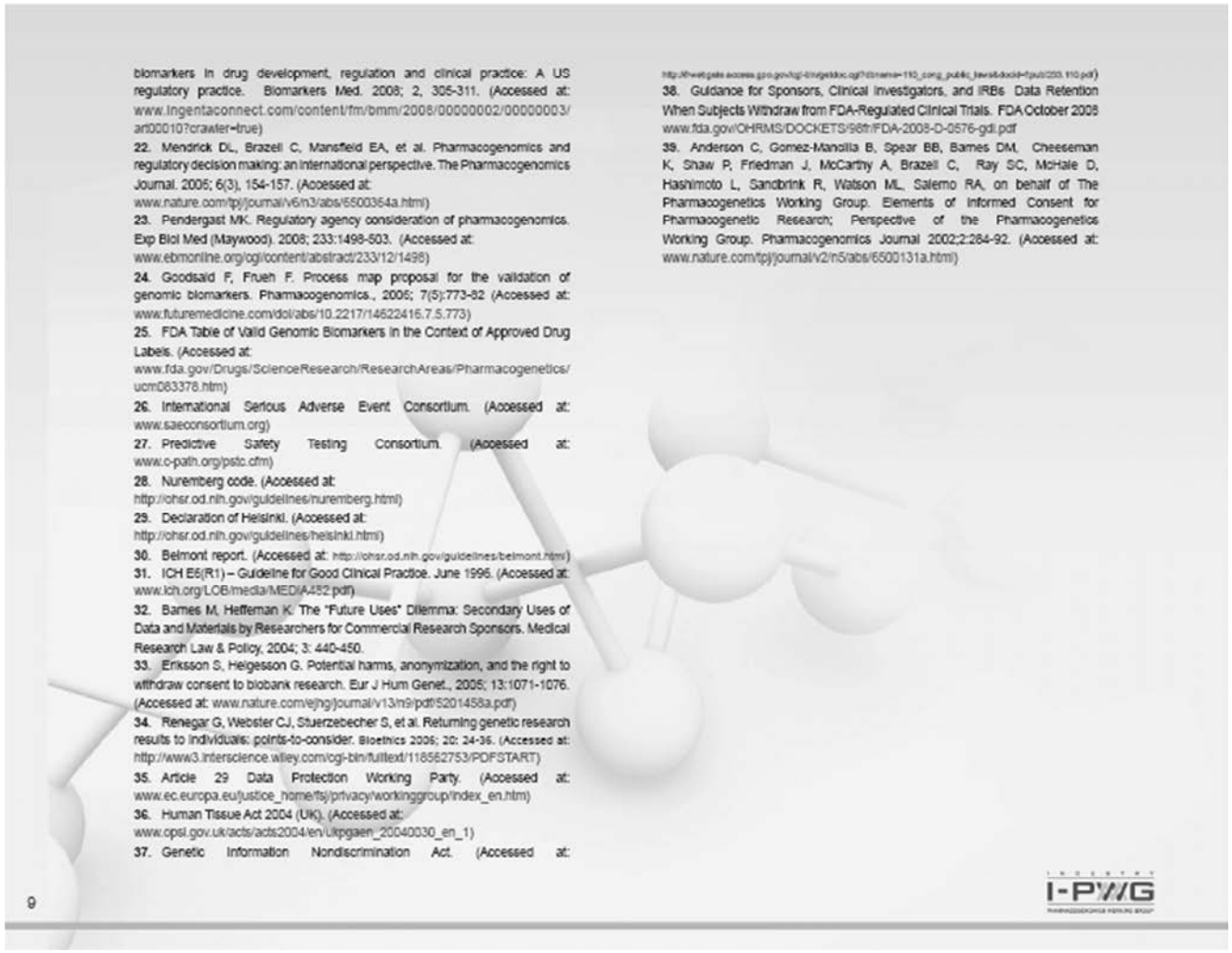

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www.i-pwg.org

12.4 Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund: fatal processes progressing rapidly
	0	Dead

Reference: http://www.hospicepatients.org/karnofsky.html

12.5 National Cancer Institute Common Terminology Criteria for Adverse Events

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse events reporting (http://ctep.cancer.gov/reporting/ctc.html).

12.6 Abbreviations

Abbreviation	Definition
ADA	anti-drug (pembrolizumab) antibodies
AE	adverse event
ALT	alanine aminotransferase
APC	antigen-presenting cells
ASaT	all subjects as treated
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration vs. time curve
β-hCG	β human chorionic gonadotropin
BCG	Bacillus Calmette-Guerin
BICR	blinded independent central imaging review/reviewer
BID	*bis in die* (twice a day)
BP	blood pressure
CAP	chest, abdomen, and pelvis
CI	confidence interval
CIV	Central Imaging Vendor
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CrCl	calculated creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	cytotoxic T lymphocytes cells
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiography
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for the Research and Treatment of Cancer

Abbreviation	Definition
EuroQol	European Quality of Life
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-related Symptoms
FSH	follicle stimulating hormone
FT3, FT4	free thyroxine
GCP	Good Clinical Practices
GI	gastrointestinal
GFR	glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HSD	Hwang-Shih-DeCani
i.e.	*id est* (that is)
IA1	first interim analysis
IA2	second interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNα	interferon alpha
IMDC	International Metastatic RCC Database Consortium
IHC	immunohistochemistry
IL-2	interleukin-2
INR	International normalized ratio
irAEs	immune-related adverse events
IRB	Institutional Review Board
irRECIST	immune-related RECIST
ITT	Intention to treat
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
KPS	Karnofsky performance status
LFT	liver function tests
mAb	monoclonal antibody
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
mRNA	messenger RNA

Abbreviation	Definition
MSI	microsatellite instability
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over the counter
PD	progressive disease or disease progression
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical exam
PFS	progression-free survival
PIN	personal identification number
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
Q	every
Q21D	every 21-day
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QALY	quality-adjusted life year
QD	*quaque die* (once a day)
QTc	QT interval corrected
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	response rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results [Program]
SNP	single-nucleotide polymorphism
SOP	standard operating procedure
sSAP	supplemental Statistical Analysis Plan
T1DM	type 1 diabetes mellitus

Abbreviation	Definition
TCR	T-cell receptors
TKI	tyrosine kinase inhibitors
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
V	volume of distribution
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell [count]

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	