Official Protocol Title:	A Phase II Single-arm, Open-label Monotherapy Clinical Trial of Pembrolizumab (MK-3475) in Locally Advanced/ Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-427)
NCT number:	NCT02853344
Document Date:	25-May-2021

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase II Single-arm, Open-label Monotherapy Clinical Trial of Pembrolizumab (MK-3475) in Locally Advanced/Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-427)

IND NUMBER: 122,753
EudraCT NUMBER: 2016-000589-47

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	25-MAY-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 03	09-NOV-2020	To remove reference to "sub-trial" in the Future Biomarker Research sections of the protocol. Revision due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a substudy to the clinical protocol.
Amendment 02	14-NOV-2017	To change the timing of bone scans at screening (accepting scans that have been performed within 42 days of screening) in order to minimize patient burden. To update the dose modification and toxicity management guidelines for pembrolizumab in order to be in alignment with the most current label and safety information for pembrolizumab.
Amendment 01	20-MAR-2017	To clarify eligibility so that inclusion and exclusion criteria are not overly restrictive. To provide a clear and concise guide to investigators on management of AEs associated with pembrolizumab. To allow enrollment in Cohort B upon local laboratory confirmation of diagnosis, and central laboratory confirmation that the submitted tissue is adequate for central review (previously, central laboratory diagnosis confirmation was required before allocation).
Original	16-JUN-2016	Not applicable

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change	Rationale
5.2.2	Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	The dose modification and toxicity management guidelines for irAEs and table were updated.	The dose modification and toxicity management guidelines for irAEs and table were updated as requested by the U.S. FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information.

ADDITIONAL CHANGE FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in advanced renal cell carcinoma
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	Phase II
Clinical Indication	Renal cell carcinoma
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	The study will include 2 cohorts 1. Clear-cell renal cell carcinoma (Cohort A) 2. Non-clear-cell renal cell carcinoma (Cohort B)
Number of trial subjects	Approximately 255 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 5 years 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 of signing the Informed Consent Form through the final protocol-specified contact. After a screening phase of 28 days, each subject will receive pembrolizumab for approximately 2 years. After the end of treatment, each subject will be followed for survival. Written consent must be obtained prior to performing any protocol-specified procedures. Informed consent may be obtained greater than 28 days prior to treatment allocation; however, it MUST be obtained prior to performing any protocol-specified procedures. Tumor tissue collection for biomarker studies and histologic confirmation of non-clear cell RCC diagnosis should be submitted after obtaining written consent; however, tissue samples may be submitted to the central laboratory greater than 28 days prior to treatment allocation. This is in order for sites to gather tumor tissue samples and/or other information from the subjects. It is recommended that the tumor samples be collected and submitted for central laboratory review as soon as the informed consent is signed.

	Study treatments will continue until progressive disease is determined, or further confirmed by the investigator, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, Investigator's decision to discontinue the subject, subject discontinuation from the study, subject receives 35 administrations of pembrolizumab (approximately 2 years), or administrative reasons requiring the cessation of treatment. Subjects who stop pembrolizumab after receiving 35 doses of pembrolizumab without progressive disease (PD), or after achieving a complete response (had a minimum of 8 administrations of pembrolizumab and at least 2 treatments beyond initial complete response [CR]) may be eligible for a second course of pembrolizumab treatment for up to 17 additional doses of pembrolizumab (approximately one year) upon experiencing PD. After the end of treatment, each subject will be followed for 30 days after the last dose of pembrolizumab for adverse event monitoring (serious adverse events will be collected up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first). Subjects who discontinue treatment for any reason other than confirmed disease progression should continue with imaging assessments per the protocol defined schedule until: 1) disease progression, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion/early termination, whichever occurs first. Following confirmation of PD, all subjects will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent from trial, loss to follow-up, or until the study is concluded or terminated early, whichever comes first. Once the study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

Randomization Ratio	Not applicable

A list of abbreviations used in this document can be found in Section 12.7.

2.0 TRIAL DESIGN

2.1 Trial Design

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

The safety and efficacy of pembrolizumab (200 mg every 3 weeks [Q3W]) will be studied in approximately 255 subjects with advanced RCC (105 subjects with clear cell (cc) RCC [Cohort A] and up to 150 subjects with non-clear cell (ncc) RCC [Cohort B]). The primary objective of the study for both cohorts is to evaluate the objective response rate (ORR), using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), as assessed by blinded independent central review (BICR). See Section 3 for a complete description of study objectives.

An interim analysis will be performed for the non-clear cell RCC cohort when the 30th subject in this cohort has had the opportunity to complete the 3rd scan. The analysis will include all scans up to this cut-off time point (see Section 8 for details). A futility check will be conducted based on the observed ORR. During the futility analysis the enrollment of subjects will continue (see Section 8 for details).

Subjects in both cohorts A and B must have confirmation of measurable disease at baseline as assessed by BICR per RECIST 1.1 and must provide an adequate tumor tissue sample for biomarker analysis in order to be eligible for the study. For Cohort B, sites will submit tissues for histologic confirmation of the diagnosis of non-clear cell RCC by central histology review during the screening phase. Sites should enroll subjects in Cohort B after receiving notice that the submitted tissue was adequate for central review. Confirmation of non-clear cell RCC histology by the central laboratory will be made available to the sites at a later date. See Section 5 for a complete list of study inclusion/exclusion criteria.

After a screening phase of 28 days, eligible subjects will receive pembrolizumab until progressive disease is initially determined or further confirmed by the investigator, unacceptable toxicity, intercurrent illness preventing further administration of treatment, investigator's decision to withdraw the subject, withdrawal of consent, noncompliance with trial treatment or procedure requirements, administrative reasons requiring the cessation of treatment, or until the subject has received 35 doses of pembrolizumab (approximately 2 years).

During the treatment period, subjects will have routine clinical visits for administering study treatment, monitoring safety and well-being, and changes in disease status. Key study safety assessments include physical examinations, vital signs, electrocardiography (ECG), hematology and chemistry laboratories including thyroid function test and urinalysis. At each visit, adverse events (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, and the dose may be withheld or discontinued upon experiencing severe AEs in accordance with the guidelines in Section 5.2.1.

Scheduled on-study imaging assessments include computed tomography (CT) and/or magnetic resonance imaging (MRI) for chest, abdomen, and pelvis. These imaging assessments will be

performed at baseline, after allocation at Week 12, then every 6 weeks (Q6W) until Week 54, and every 12 weeks (Q12W) thereafter. Baseline bone scans will be performed for all subjects at screening. Bone scans are not required to be repeated at screening if performed within 42 days prior to treatment allocation. If a subject has a positive bone scan at screening, bone scans will be performed at Weeks 18, 30, 42, and 54, and then every 24 weeks (Q24W) thereafter. For indeterminate bone lesions at baseline, these lesions should be followed according to the bone scan imaging time points until these lesions are determined non-cancerous. In addition, a bone scan is also required for confirmation of a complete response. Additional imaging for baseline and follow up may be required if lesions outside the aforementioned regions are identified. See Section 7.1.2.7 for details.

Imaging assessments will be performed according to the aforementioned schedule regardless of study treatment status until PD is initially determined or further confirmed by the investigator, initiation of another anti-cancer therapy, death, withdrawal of consent from the trial or study conclusion or early termination, whichever occurs first. All disease assessment imaging scans must be submitted promptly to the designated central imaging vendor.

For both cohorts when a subject is identified with PD by the site investigator/radiologist, PD will be confirmed by subsequent scans at the site (for subjects who are clinically stable). Subjects who are clinically stable may also continue on treatment at the discretion of the investigator until progression is confirmed with a repeat scan. Details are provided in Sections 7.1.2.7.2 and 7.1.2.7.6.

For the non-clear cell cohort (Cohort B), when a subject is identified with PD by the site investigator/radiologist, the site will submit scans to the central imaging vendor for PD verification by BICR. Subjects who are clinically stable may continue on treatment at the discretion of the investigator while awaiting verification of PD by BICR. Following PD verification by BICR, subjects who are clinically stable may continue on treatment until progression is confirmed by subsequent scans at the site. Details are provided in Sections 7.1.2.7.2 and 7.1.2.7.6.

In the event that a subject has experienced a partial response (PR) or CR, confirmation of response should be performed at the next scheduled imaging assessment visit. Refer to Section 7.1.2.7.2 for details pertaining to confirmation of response.

After 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.

All AEs and events of clinical interest (ECIs) occurring within 30 days after the last dose of trial treatment must be recorded regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs occurring up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur (see Sections 7.2.3.1 and 7.2.3.2 for further details regarding serious adverse events (SAEs) and ECIs reporting).

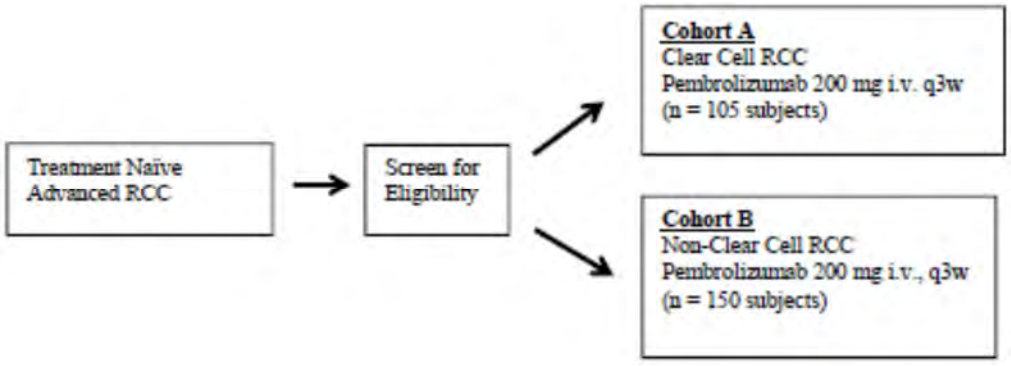
Subjects who discontinue for reasons other than disease progression will stay on study and will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up, or death. All

subjects will be followed by telephone or clinic visit for overall survival until death, withdrawal of consent, loss to follow-up, or the end of the study.

In the event that a 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 and at least 2 treatments beyond initial CR). Subjects who discontinue after 35 doses/infusions for reasons other than disease progression or intolerability, or who discontinue after attaining a CR [and had at least 2 treatments beyond initial CR] may be eligible for up to 17 additional doses of pembrolizumab after they have experienced radiographic disease progression. The decision to re-treat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open (refer to Section 7.1.5.2.1 for further details).

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



- Treatment will continue until disease progression, prohibitive toxicity, death, withdrawal of consent or until 35 infusions/doses of pembrolizumab have been administered.
- Radiographic disease assessments will be performed at Week 12, then every 6 weeks until Week 54, then every 12 weeks thereafter. Unscheduled imaging can be performed as clinically indicated.
- Primary endpoint is ORR by RECIST 1.1

Subjects who discontinue treatment for reasons other than disease progression should continue with imaging assessments per the protocol-defined schedule until disease progression, initiation of a new anti-cancer treatment, death, withdrawal of consent or study conclusion or early termination, whichever occurs first.

For the non-clear cell cohort (Cohort B), 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.

Figure 1 Study Schema

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

There will be no formal hypothesis testing in this study.

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To estimate the ORR per RECIST 1.1 as assessed by BICR in subjects with clear cell RCC.

(2) **Objective:** To estimate the ORR per RECIST 1.1 as assessed by BICR in subjects with non-clear cell RCC.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:** To estimate the duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) per RECIST 1.1 as assessed by BICR and overall survival (OS) in subjects with clear cell or non-clear cell RCC by cohort.

(2) **Objective**: To determine the safety and tolerability of pembrolizumab in subjects with clear cell or non-clear cell RCC by cohort.

(3) **Objective:** To describe the patient population using the International Metastatic RCC Database Consortium (IMDC) risk group (see Section 12.5 for IMDC criteria): favorable versus intermediate versus poor risk groups in subjects with clear cell or non-clear cell RCC by cohort [1] [2] [3].

3.3 Exploratory Objectives

(1) **Objective:** To estimate ORR, DOR, DCR, and PFS per RECIST 1.1 as assessed by BICR and OS by centrally determined tumor programmed death-ligand 1/2 (PD-L1/2) status in subjects with clear cell or non-clear cell RCC by cohort.

(2) **Objective:** To estimate ORR, DOR, DCR, and PFS per RECIST 1.1 assessed by BICR and OS for patients with any sarcomatoid differentiation identified by cohort.

(3) **Objective:** To evaluate pharmacokinetic (PK) parameters and the presence of anti-drug antibodies in subjects by cohort.

(4) **Objective:** To estimate ORR, DOR, DCR, and PFS per immune-related RECIST (irRECIST) by BICR in subjects with clear cell or non-clear cell RCC by cohort.

(5) **Objective:** To identify molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to pembrolizumab in clear cell or non-clear cell RCC so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

Disease Background:

Advanced Renal Cell Carcinoma (RCC)

Epidemiology and Disease Characteristics of RCC

RCC 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 64% of patients have localized disease; 17% 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 presence of distant metastasis [6].

Current Systemic Treatments for Advanced RCC

Advanced RCC has previously been treated with immunotherapies such as interferon alpha (IFNα) and interleukin 2 (IL-2) with limited clinical activity. A novel group of anti-cancer agents has been developed for the treatment of advanced RCC since 2005. These agents demonstrate significant improvement in clinical efficacy and have acceptable safety profiles. They include vascular endothelial growth factor receptor (VEGFR) TKIs (sunitinib, pazopanib, sorafenib, and axitinib), an anti-VEGF monoclonal antibody (bevacizumab given in combination with IFNα), and mammalian target of rapamycin inhibitors (temsirolimus and everolimus). Recently, the PD-L1 checkpoint inhibitor nivolumab received approval from the Food and Drug Administration (FDA) to treat patients with advanced RCC whose disease progressed on an anti-angiogenic therapy [7].

Clinical Trials and Recommended Treatments for Renal Cell Carcinoma

Clinical Trials in Treatment-Naïve Advanced RCC

Table 1 summarizes the clinical efficacy of systemic treatments in patients with treatment-naïve advanced clear cell 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 EMA for the treatment of advanced RCC in treatment-naïve patients without regard to histology, as each demonstrated a statistically significant improvement in PFS compared to IFNα or placebo alone. 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 for first-line treatment of poor-risk patients with advanced RCC without regard to histology.

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; RCC=renal cell carcinoma.

a Results demonstrated statistically significant improvement of the testing arm versus 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.

National Comprehensive Cancer Network and European Society for Medical Oncology Recommended First Line Treatments for Advanced Clear Cell RCC

Based on the data described above, the current recommendations by National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) for first-line treatment of advanced clear cell 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 two 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*=.0006) [15].

Clinical Studies in the Previously Treated Advanced Clear Cell Renal Cell Carcinoma Population

Sorafenib was approved by the FDA for advanced RCC without regard to histology based on a phase III randomized trial by demonstrating significant improvement in PFS compared to placebo in patients having received one prior systemic therapy. The median PFS for sorafenib compared to placebo was 167 days versus 84 days, respectively (HR: 0.44; 95% CI: 0.35 to 0.55) [17]. Patients receiving placebo were recommended to cross over to the sorafenib treatment arm. After censoring of crossover data, treatment with sorafenib was shown to improve survival (17.8 months versus 14.3 months for sorafenib and placebo, respectively; HR: 0.78; 95% CI: 0.62 to 0.97, *P*=.029) [17].

Everolimus was approved by the FDA and EMA for the treatment of advanced RCC without regard to histology after failure of treatment with sunitinib or sorafenib based on a Phase III randomized trial that demonstrated a statistically significant improvement in PFS. The median PFS was 4.9 months versus 1.9 months in the everolimus and placebo groups, respectively (HR: 0.33; 95% CI: 0.25 to 0.43; *P*<.001). The final median OS was 14.8 months for everolimus versus 14.4 months for placebo (HR: 0.87; 95% CI: 0.65 to 1.15; *P*=.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 versus sorafenib (median PFS 6.7 versus 4.7 months; HR: 0.665; 95% CI: 0.544 to 0.812; *P*<.0001). The secondary endpoint of ORR was also significantly higher in axitinib versus sorafenib (19% versus 9%; *P*=.0001) [20]. However, the final OS data showed no significant difference between the two arms; median OS was 20.1 months for axitinib versus 19.2 months for sorafenib (HR: 0.969; 95% CI: 0.800 to 1.174; one-sided *P*=.3744) [21]. Based on these data, axitinib gained approval for use in advanced RCC patients after failure of one prior systemic treatment (FDA) (INLYTA Label) or after failure of sunitinib or cytokine therapy (EMA) without regard to histology [22] [23].

Recently, nivolumab, an immune checkpoint inhibitor targeting programmed cell death protein 1 (PD-1), has received approval from the FDA for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy without regard to RCC histology [7]. The approval was based on data from a randomized Phase III open-label study in advanced RCC patients following prior treatment with targeted therapy. Nivolumab demonstrated statistically significant improvement in the primary endpoint OS versus everolimus during the planned interim analysis (median 25.0 versus 19.6 months; HR: 0.73; 98.5% CI: 0.57 to 0.93; *P*=.002). The objective response rate was 25% for nivolumab versus 5% for everolimus (odds ratio 5.98; 95% CI: 3.68 to 9.72; *P*<.001). Progression-free survival was not significantly improved (median 4.6 months for nivolumab versus 4.4 months for everolimus; HR: 0.88; 95% CI: 0.75 to 1.03; *P*=.11) [24].

NCCN and ESMO Recommended Subsequent Treatments for Advanced Clear Cell RCC

Subsequent treatments following the failure of first-line have been divided into two categories: treatment choices after prior cytokine therapy and treatment choices after prior targeted therapy. Axitinib, sorafenib, sunitinib, and pazopanib have demonstrated improved efficacy (PFS) in the cytokine failure population and, hence, have been recommended by NCCN and ESMO for use in this population [4] [6]. However, cytokine use in the first-line 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.

In addition, NCCN has recently recommended cabozantinib as a treatment choice after prior targeted therapy [6]. Cabozantinib is a multi-target tyrosine kinase inhibitor targeting VEGFR, MET, and AXL. In a Phase III randomized trial versus everolimus in patients who failed prior targeted therapy, cabozantinib demonstrated significantly improved primary endpoint PFS (median 7.4 versus 3.8 months; HR: 0.58; 95% CI: 0.45 to 0.75; *P*<.001) and secondary endpoint ORR (21% versus 5%; *P*<0.001). The interim OS (49% full information) showed a trend favoring cabozantinib but did not reach pre-defined statistical significance (HR: 0.67; 95% CI: 0.51 to 0.89; *P*=.0050) favoring cabozantinib. The criteria for early rejection of the hypothesis was not met (P≤.0019) [25]. As of April 2016, cabozantinib has been approved for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy [26].

Clinical Trials and Recommended Treatments for Non-Clear Cell RCC

Clinical Trials in Treatment-Naïve Advanced Non-Clear Cell RCC

Because of the low prevalence of nccRCC, it is difficult to accrue enough patients for a large Phase III trial. All registration trials in advanced RCC described above, with the exception of the temsirolimus registration trial, were limited to clear cell or predominately clear cell histology. Evidence for efficacy in nccRCC therefore comes either from the retrospective subset analysis of the temsirolimus Phase III trial in poor risk patients or data from small Phase II trials.

A retrospective subgroup analysis of different tumor histologies of the Phase III trial of temsirolimus vs IFNα cited above [16] demonstrated a median OS of 11.6 months (95% CI: 8.9 to 14.5, N=37) in the temsirolimus arm compared to a median OS of 4.3 months (95% CI: 3.2 to 7.3, N=36) in the IFNα arm [27]. In the ASPEN trial, 108 patients with nccRCC were randomized to treatment with sunitinib or everolimus and the median PFS was found to be 8.3 months and 5.6 months, respectively (HR: 1.41; 80% CI: 1.03 to 1.92; *P*=.16) [28]. In a non-randomized Phase II study (SUPAP) conducted by the French Genitourinary Group, 61 subjects with papillary RCC, 15 with type 1 and 46 with type 2, were treated with sunitinib. Objective response rates of 13% and 11% were reported, respectively. Median PFS was 6.6 months (95% CI: 2.8 to 14.8) in type 1 and 5.5 months (95% CI: 3.8 to 7.1) in type 2 [29]. In a single-arm Phase II study, 46 subjects with advanced or metastatic papillary RCC were treated with erlotinib. The ORR was 11% (95% CI: 3 to 24%) with a disease control rate (defined as stable disease for 6 weeks or CR or PR per RECIST 1.1) of 64%. The median OS was 27 months (95% CI: 13 to 36 months) [30].

NCCN and ESMO Recommended First Line Treatments for Advanced Non-Clear Cell RCC

Due to limited data in nccRCC patients, the role of various agents in the treatment of nccRCC is poorly defined and there is no standard of care. As such, the NCCN consensus guidelines state that enrollment in clinical trials is the preferred strategy for subjects with nccRCC [6].

Because there is some evidence from the Phase III temsirolimus trial demonstrating that subjects with poor prognosis risk factors may benefit from treatment with temsirolimus compared to IFNα, NCCN recommends this agent for this clinical setting. Of note, this was

not a pre-specified analysis but rather a retrospective analysis of these two arms of the trial (temsirolimus N=37, interferon alpha N= 36) [27]. The NCCN guidelines list everolimus, sorafenib, bevacizumab, pazopanib, and axitinib as other agents that may be used in the first-line treatment of nccRCC. The sorafenib North American expanded access program enrolled subjects with advanced disease without regard to number of prior lines of therapy. Subjects with papillary nccRCC (N= 107) had a response rate of 3% and clinical benefit rate (CR+PR +stable disease>8 weeks) of 84%. Subjects with chromophobe nccRCC had a response rate of 5% and clinical benefit rate of 90% [31]. Bevacizumab is included as a possible agent due to results of a small Phase II study that closed due to poor accrual. The PFS from 5 subjects treated with bevacizumab are reported as 25, 15, 11, 10, and 6 months [32]. Although data are not yet available from ongoing clinical trials, pazopanib and axitinib are included in the guidelines by extrapolation of their effects in clear cell RCC.

Based on the same dataset as above, ESMO guidelines recommend temsirolimus, sunitinib or sorafenib for the first-line treatment of nccRCC [4].

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Targeting PD-1 Immune Checkpoints for Cancer Treatments

The adaptive immune system plays a major role in controlling and eradicating cancer in 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 (APC) [33] [34] [35].

T cell activation is tightly controlled by co-stimulatory and co-inhibitory signals which are triggered by the interactions between T cell receptors (TCR) 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. PD-1 is a member of the extended CD28/CTLA4 family of T cell regulators. Activation of the 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 ligand PD-L1 and/or 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 [33] [36] [37] [38]. PD-L1 was found expressed on the surface of many human cancer cells; and PD-L1 expression by tumor cells was found associated with poor progression in several cancers including RCC [39].

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, in particular the PD-1 inhibitors, has significantly changed the landscape of cancer treatment [34] [35] [36] [40] [41] [42] [43].

4.1.1.2 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 has received accelerated approval for the treatment of 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 two indications is 2 mg/kg Q3W [44].

4.1.1.3 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 week (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 [45]. 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 two 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 [46].

Clinical efficacy of pembrolizumab in advanced melanoma was further demonstrated via two 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 two pembrolizumab arms compared with the chemotherapy arms. 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 ($P<.0.001$ 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 two pembrolizumab arms, respectively, versus 63% in the chemotherapy arm. There was no statistically significant difference in efficacy parameters between the two pembrolizumab arms [47].

In 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 [48].

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), the ORR was 19.4% (95% CI: 16.0 to 23.2) and the median DOR was 12.5 months. In the validation data set, the 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); the 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 [49].

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 who 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 track cancer, and triple negative breast cancer were enrolled. An ORR of 31% was observed in subjects with advanced gastric cancers (N = 39) [50]; an ORR of 27.6% (95% CI: 12.7 to 47.2%) was observed in subjects with advanced urothelial tract cancer (N = 33) [51]; an ORR of 24.8% (95% CI: 17.3 to 33.6%) was observed in subjects with advanced head and neck cancer (N = 132) [52]. Impressive responses have also been reported by Nanda et al., in triple negative breast cancer at the 2014 San Antonio Breast Cancer Symposium [53]. In all these cohorts, durable responses were observed in those who responded, including some durable stable diseases. Higher PD-L1 expression seemed to be associated with higher response.

Preliminary clinical activity of pembrolizumab in combination with axitinib in advanced RCC

Pembrolizumab monotherapy has not been evaluated in advanced RCC. However, the pembrolizumab and axitinib combination has recently been evaluated in treatment-naïve subjects with advanced RCC. 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 maximum tolerated doses were determined to be 5 mg twice a day (BID) by mouth (PO) for axitinib and 2 mg/kg Q3W intravenous (IV) for pembrolizumab.

A total of 52 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 cut off of March 2016 (data not published). The demographic features are typical for advanced RCC population: median age was 61.2, 78.8% male and 86.5% white. All had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 1. Of the 52

patients, 12 had discontinued pembrolizumab treatment: 7 (13.5%) due to AEs, 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 are: all grade, 100%; grade 4, 3.8%; grade 3, 53.8%; grade 2, 32.7% and grade 1, 9.6%. There was 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	Total	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

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

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

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

Based on the scientific rationale of targeting angiogenesis and immune-check point pathways, as well as the promising data from these 52 patients, a phase III study is planned to evaluate the pembrolizumab/axitinib combination versus sunitinib in the first line treatment of metastatic clear cell renal cell carcinoma.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Renal cell carcinoma 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 [49] 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 the PD-1 receptor on tumor-infiltrating lymphocytes and its ligand PD-L1 on tumors is associated with more aggressive disease and poor prognosis [38] [54]. The evidence above supports targeting RCC with an immunotherapeutic approach. Single agent anti-tumor activity has been demonstrated by another anti-PD-1 antibody, nivolumab, in advanced RCC [24].

Even though the successful clinical development of 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, most patients will progress within 2 years following a standard first-line treatment. As of now, the best median overall survival seen with the 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. in 645 patients who received first-line anti-VEGF/VEGFR agents including sunitinib, sorafenib, and bevacizumab in the US and Canada, the median survival was 22 months [1]. Based on Surveillance, Epidemiology, and End Results data from 2004-2010, the 5-year survival rate of advanced RCC was only 12% [5]. Therefore, further development of novel agents, such as pembrolizumab, with durable clinical benefit and potential curative effect is still highly needed for advanced RCC.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Rationale for using 200 mg Q3W dose for pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.

Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010 and KN021), and

three studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy endpoint, objective response rate (ORR), as well as the secondary endpoints of DOR, disease control rate (DCR), progression-free survival (PFS), all as assessed by BICR per RECIST 1.1, and overall survival (OS) are acceptable endpoints to support approval of new treatments in advanced RCC. Durable response has been demonstrated with pembrolizumab and other immune checkpoint inhibitors in a subset of patients in multiple tumor types and these endpoints will provide meaningful supporting evidence for clinical efficacy. In order to avoid PD being called prematurely by the investigator, subjects in Cohort B with suspected radiologic progression first identified at the site will have all the scans submitted to the BICR for verification of PD. The results of central PD verification will be communicated to the site promptly.

4.2.3.1.1 Immune-related RECIST

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 can 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 PD by RECIST 1.1 but not by immune-related Response Criteria had longer OS than patients with PD 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 an adjustment 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., CCR 2013 [55]. 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. Immune-related RECIST will be used by local site investigators to assess tumor response and progression, and 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 subjects with advanced RCC as first line treatment. The following safety parameters will be analyzed: adverse events and serious adverse events graded per National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (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. (Section 12.6). Concomitant medications will be collected with time and reasons of use. These are routine safety parameters collected and analyzed in Phase II oncology trials. Furthermore, specific immune-related adverse events (irAEs) will be collected as described in Section 7.1.2.1.

4.2.3.3 Planned Exploratory Biomarker Research

Introduction: Cancer immunotherapies are an important novel class of anti-tumor agents. However, much remains to be learned about how cancer immunotherapies work and how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of adverse events in the course of our clinical trials. To that end we seek to define novel predictive/pharmacodynamic biomarkers and the best strategies of combination therapy with immuno-oncology drugs. To fully leverage the clinical data collected in this trial, we will also collect biospecimens (blood components, tumor material, etc) to support biomarker analyses of cellular components (e.g., protein, deoxyribonucleic acid [DNA], ribonucleic acid [RNA], metabolites) and other blood soluble molecules. Investigations may include but are not limited to:

Germline (blood) Genetic Analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of

therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

Genetic (DNA) analyses from tumor: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability, etc). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) is one of the major mechanisms of neo-antigen presentation in the context of a tumor microenvironment. There is a potential that in the hyper-mutated state, the presence of neo-antigen mutational patterns and the detection of increased T-cell clonality, both of which can be determined by use of next-generation sequencing methods, may correlate with response to pembrolizumab therapy and/or that the converse, the "hypomutated" state (the absence of neo-antigens) may correlate with non-response. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome. Microsatellite instability (MSI) may also be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

Tumor and blood RNA analyses: Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL-10). MicroRNA profiling may also be pursued.

Proteomics and Immunohistochemistry (IHC) using Blood or Tumor: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., TNBC, H&N, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood derived biomarkers: In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunosorbent assay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on

assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.3.4 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 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

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab has been administered to a large number of cancer subjects with a well characterized safety profile and has received regulatory approval for advanced melanoma and NSCLC. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg Q2W. Pembrolizumab has also demonstrated anti-cancer clinical activity and efficacy in a broad range of cancer indications (see Summary in Section 4.1.2.3).

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.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with advanced renal cell carcinoma (RCC) at least 18 years of age 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. Cohort A (clear cell cohort) must have histologically confirmed diagnosis of clear cell RCC or RCC with clear cell component (with or without sarcomatoid features). Diagnosis of clear cell RCC is to be made by the site and does not require central histology review.
4. Cohort B (non-clear cell cohort) must have histologically confirmed diagnosis of non-clear cell RCC (with or without sarcomatoid features) by the site pathologist. For Cohort B, sites will submit tissues for histologic confirmation of the diagnosis of non-clear cell RCC by central histology review during the screening phase. Sites should enroll subjects in Cohort B after receiving notice that the submitted tissue was adequate for central review. Confirmation of non-clear cell RCC histology by the central laboratory will be made available to the sites as a later date. (See Section 7.1.3.3 and the Procedures Manual for further details). Subjects with tumors that have a component of clear cell histology are not eligible for inclusion in Cohort B. (Subjects with a clear cell component will be eligible for Cohort A assuming all other entry criteria are met.)
5. Have locally advanced/metastatic disease, i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer (AJCC) or have recurrent disease.
6. Have measurable disease per RECIST 1.1 as assessed by BICR. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Have received no prior systemic therapy for advanced RCC.

   Note: Prior neoadjuvant/adjuvant therapy for RCC is acceptable if completed > 12 months prior to allocation.
8. Provide adequate tissue for biomarker analysis for cohorts A and B from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Adequacy of these samples for PD-L1 biomarker analysis will be evaluated by a central laboratory and is required for enrollment. NOTE: If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from the date the slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).
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 treatment allocation.
10. Have Karnofsky Performance Status (KPS) ≥70%, as assessed within 10 days prior to treatment allocation (see Section 7.1.2.6 for more details).

11. Demonstrate adequate organ function as defined in Table 4 and all screening laboratory tests should be performed within 10 days of treatment initiation.

Table 4 Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mm^3 or ≥ 1.5 x 10^9 / L
Platelets	≥100,000 / mm^3 or ≥ 100 x 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[a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥40 mL/min for subjects with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with active liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN subject receiving anticoagulant therapy can have INR exceed 1.5 x ULN as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT) or PTT	≤1.5 X ULN

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Creatinine clearance should be calculated per institutional standard.

12. Female subject of childbearing/reproductive potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

13. 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.

14. 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 using an investigational device within 4 weeks prior to allocation, has had major surgery within 4 weeks or radiation therapy within 2 weeks prior to allocation, or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to prior treatment.
2. 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, GITR.
3. Has a diagnosis of immunodeficiency; OR is receiving a systemic steroid therapy exceeding 10 mg daily dose of prednisone or equivalent or any other form of immunosuppressive therapy within 7 days prior to allocation, except in the case of central nervous system (CNS) metastases (see Exclusion Criterion 6).
4. 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 a documented history of clinically severe autoimmune disease.

   Note: Subjects with vitiligo, Sjøgren's syndrome, Type I 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 would 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.

5. Has a known additional malignancy that has had progression or has required active treatment in the last 3 years.

   Note: Basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, such as breast cancer in situ, that has undergone potentially curative therapy are acceptable.

6. 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 the repeat

imaging should be performed during study screening), clinically stable and without requirement of steroid treatments for at least 14 days prior to first dose of trial treatment.

7. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
8. Has an active infection requiring systemic therapy.
9. 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 patient has Human Immunodeficiency Virus infection or is otherwise mandated per local guidance.

10. Has a known history of hepatitis B (e.g., Hepatitis B surface antigen (HBsAG) reactive or known active hepatitis C virus (e.g., 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.

11. Has received a live virus vaccine within 30 days of treatment allocation (See Section 5.5.3 – Prohibited Concomitant Medications for further details).
12. 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.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Has had a prior solid organ transplant.
15. 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

The treatment to be used in this trial is outlined below in Table 5.

Table 5 Trial Treatment

Treatment	Regimen	Route of Administration	Duration of treatment	Use in Study
Pembrolizumab	200 mg every 3 weeks (Q3W)	Intravenous infusion	Up to 35 doses (approximately 24 months)[a]	Experimental

[a] Upon progression, subjects may receive a second course of pembrolizumab treatment with additional 17 doses. Details are described in Section 7.1.5.2.1.

Trial Treatment should begin within 3 days of allocation.

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 pembrolizumab monotherapy to be used in this trial is provided in Section 4.0 – Background and Rationale. Details on the preparation and administration of pembrolizumab is in the Pharmacy Manual.

5.2.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. 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 study 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, 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 monotherapy, coformulations, or IO combinations are provided in Table 6.

A decrease or increase of the dosage of pembrolizumab is not permitted. The pembrolizumab cycle visits/procedures will remain fixed and will not be adjusted for dosing interruptions or delays. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring 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
	Recurrent Grade 2 or Grade 3 or 4	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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring 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	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• 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 [a]		
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 [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management Infusion Reactions Related to Pembrolizumab

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

Table 7 Pembrolizumab 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 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 1.5h (± 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 and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in subject's study record.

5.2.3 Timing of Dose Administration

The first dose of pembrolizumab infusion will be administered on Cycle 1 Day 1 but no later than Cycle 1 Day 4. Subsequent doses of pembrolizumab will be administered on Day 1 of each 21-day cycle (+/- 3 days). If pembrolizumab has been withheld due to toxicity or other

allowed reasons and subsequently can be resumed, the day of next pembrolizumab dose should counted as Day 1 (± 3 days) of the next cycle.

Pembrolizumab should be administered after all pre-dose study procedures and assessments have been completed as specified in the trial flow chart (Section 6.0).

Pembrolizumab should be administered as a 30-minute IV infusion every 3 weeks. 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 of the study treatment infusion fluid and administration of infusion solution.

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 or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

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 study intervention or vaccination may be required. The investigator is to discuss prohibited medication/vaccination 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 case report form (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. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 7.2.

Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.5.2 Concomitant Surgery

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.

5.5.3 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during study treatment period (including retreatment 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 on an exceptional case-by-case basis after consultation with Sponsor. The radiation treatment field may not include a target or measurable lesion by RECIST 1.1.

- Live or live-attenuated vaccines within 30 days prior to the first dose of pembrolizumab and through 30 days following the last dose of pembrolizumab. Notes: Killed virus vaccines are allowed.

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

- Systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - As needed for the prevention of emesis
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for COPD exacerbations
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
  - In addition, the following glucocorticoid use is allowed:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

    Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., IV contrast dye or transfusions) is permitted.

    Note: The use of intermittent inhaled steroids or intranasal or local injection of corticosteroids is permitted. Topical corticosteroids are also permitted.

Note: The use of physiologic doses of corticosteroids under other circumstances may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require additional anti-cancer treatments will be discontinued from study treatments and continue on survival follow up. Subjects, who in the assessment by investigator, require any other prohibited medications for 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 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, (Table 6). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 6 in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

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 (one 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 two 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, 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 must be 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 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 of consent.

As certain data on clinical events beyond study treatment discontinuation may be 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 be monitored in the study and participate in the trial visits and procedures as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1 Withdraw/Discontinuation.

Subjects may discontinue study treatment at any time for any reason or be discontinued 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 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 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.
- After receiving 35 doses of pembrolizumab

When a subject is first identified with radiologic PD by the investigator, all scans for subjects in Cohort B 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 of PD 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 7.1.2.7.2.

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) disease progression (refer to Section 7.1.2.7.2), 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 of Consent

Subjects may withdraw consent at any time for any reason. If a subject withdraws consent, 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.

5.9 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 last subject completes the last study-related phone-call or visit, withdraws consent or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

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 safety by the Sponsor
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

Trial Period:	Screening	Treatment Cycles												End of Treatment	Post-Treatment Visits		
		Cycles 1 to 8								Beyond Cycle 8							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days) [a]	Every 12 weeks (± 7 days)[b]
Administrative Procedures																	
Informed Consent (may be done prior to screening period)[c]	X[c]																
Informed Consent for Future Biomedical Research (optional)	X																
Inclusion/Exclusion Criteria	X																
Subject Identification Card[d]	X													X			
Demographics and Medical History	X																
Prior and Concomitant Treatment/Medication Review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration		X[f]	X	X	X	X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status															X	X	X
Survival Status[b]		<----------												---------->			X
Clinical Procedures/Assessments																	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	
Full Physical Examination	X													X			
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram (locally performed)[i]	X																
Karnofsky Performance Status[j]	X		X	X	X	X	X	X		X		X			X		

Trial Period:	Screening	Treatment Cycles												End of Treatment	Post-Treatment Visits		
		Cycles 1 to 8								Beyond Cycle 8							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days) [a]	Every 12 weeks (± 7 days)[b]
Efficacy Measurements																	
Tumor Imaging - chest, abdomen, pelvis (CAP)	X[k]	X[l]														X[m]	
Tumor Imaging – bone scan[n]	X[n]	X[n]														X[n]	
Tumor imaging – brain scan[o]	X[o]	X[o]															
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																	
Pregnancy Test – Urine or Serum β-HCG[p]	X																
PT/INR and aPTT[q]	X		X	X	X	X	X	X		X		X		X	X		
Hematology[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[q]	X		X	X	X	X	X	X		X		X		X	X		
T3, FT4, and TSH[q]	X		X	X	X	X	X	X		X		X		X	X		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory																	
Anti-pembrolizumab Antibodies (ADA)[r]		X		X		X				X					X		
Pharmacokinetics (PK)[r,s]		X		X		X				X					X		
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																	
Archival or Newly Obtained Tissue Collection for biomarkers studies (may be done prior to screening period)[c,t]	X[c,t]																
Tissue for central histologic confirmation of nccRCC diagnosis (may be done prior to screening period)[c,t, u]	X[c,u]																
Blood for Genetic Analyses[v]		X															

Trial Period:	Screening	Treatment Cycles												End of Treatment	Post-Treatment Visits		
		Cycles 1 to 8								Beyond Cycle 8							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days) [a]	Every 12 weeks (± 7 days)[b]
Blood for ctDNA Analyses[w]		X	X			X								X			
Blood for TCR repertoire[w]		X	X			X								X			
Blood for RNA Analyses[w]		X	X			X								X			
Blood for plasma biomarker Analyses[w]		X	X											X			
Blood for serum biomarker Analyses[w]		X	X											X			

a. Efficacy Follow-up visits will continue on the same schedule that the subject is on at the time of discontinuation from treatment, every 6 weeks from allocation (Q6W, 42 days ± 7 days) through week 54 and every 12 weeks (Q12W, 84 days ± 7 days) thereafter. After Week 104 from allocation, the window for Efficacy Follow-up is ± 14 days. See Section 7.1.5.3.3 for details on data collected.

b. The Survival Follow-up may be conducted as a telephone call or a clinic visit approximately Q12W (visit window is ± 7 days through Week 104 and ± 14 days after Week 104). 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. Written consent must be obtained prior to performing any protocol-specified procedures. Informed consent may be obtained greater than 28 days prior to treatment allocation; however, it MUST be obtained prior to performing any protocol-specified procedures. This is in order for sites to gather tumor tissue samples and/or other information from the subjects. It is recommended that the tumor samples be collected and submitted for central laboratory review as soon as the informed consent is signed.

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

e. 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.

f. Cycle 1 treatment must be given within 3 days of treatment allocation.

g. Record all AEs and ECIs occurring within 30 days after the last dose of trial treatment regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs occurring up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur (see Sections 7.2.3.1 and 7.2.3.2 for further details regarding SAE and ECI reporting).

h. Height will be measured at screening visit only.

i. Electrocardiogram (ECG) will be performed at screening for all subjects and as clinically indicated thereafter.

j. Karnofsky Performance Status will be assessed at screening (within 10 days of treatment allocation), on Day 1 of Cycles 2 – 7, every other cycle thereafter (C9D1, C11D1, C13D1…) and Safety Follow-up. See Appendix 12.4.

k. Baseline CAP imaging must be performed within 28 days prior to treatment allocation. 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 28 days prior to allocation. See Section 7.1.2.7.1 for additional imaging requirement in subjects with RCC metastatic lesions identified outside of the standard imaging assessment anatomic regions per protocol BICR assessment will be used to determine eligibility for both Cohorts.

Trial Period:	Screening	Treatment Cycles												End of Treatment	Post-Treatment Visits		
		Cycles 1 to 8								Beyond Cycle 8							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days) [a]	Every 12 weeks (± 7 days)[b]

l. Imaging after allocation will be performed at Week 12 (Day 84 ± 7 days, then every 6 weeks (42 days ±7 days) until Week 54, then every 12 weeks (84 days ±7 days) thereafter until PD is confirmed by the investigator for Cohort A and BICR verified followed by further confirmation by the investigator for Cohort B (see Section 7.1.2.7.2 for details). The imaging visit window can be ± 14 days after two years on study. Imaging anatomic coverage should be the same as that at screening; see Section 7.1.2.7.2 for detail. Unscheduled imaging can be performed as clinically indicated. The timing of imaging assessments should follow calendar days from allocation and should not be adjusted for dose delays or cycle starts

m. Subjects who discontinue from study medication without documented disease progression should continue with radiographic imaging (CT/MRI and bone scans, if applicable) until 1) the start of new anti-cancer treatment, 2) documented disease progression per 7.1.2.7.2, 3) death or 4) withdraw of consent 5) study conclusion or early termination, whichever occurs first. See footnote "a" for Efficacy Follow-up schedule and windows.

n. Baseline bone scan will be performed for all subjects at Screening. Bone scans are not required to be repeated at screening if performed within 42 days prior to treatment allocation. If a subject has a positive bone scan at Screening, on-study bone scans should be performed at the end of 18 weeks from treatment allocation (126 ± 7 days). Bone scans should continue to be performed Q12W (84 days ±7 days) through Week 54. After Week 54, subjects will have bone scans performed every 24 weeks (168 days ±7 days). The timing of imaging assessments should follow calendar days from allocation and should not be adjusted for dose delays or cycle starts. A bone scan must also be performed for confirmation of Complete Response (CR).

o. 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.

p. 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.

q. PT/INR and aPTT, urinalysis and thyroid function testing will be performed at Screening (within 10 days of allocation), on Day 1 of Cycles 2-7, every other cycle thereafter (C9D1, C11D1, C13D1,…), End of Treatment visit and at the Safety Follow-up visit. Hematology and chemistry will be performed at Screening (within 10 days of allocation), on Day 1 of every treatment cycle from Cycle 2 onwards, the End of Treatment visit, and the Safety Follow-up visit.

r. Pre-dose trough PK and ADA samples 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.

s. Post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 9.

t. For both Cohort A and B adequacy of tissue samples for PD-L1 biomarker analysis will be evaluated by a central laboratory during the screening period. It is a requirement for enrollment that the tissue be adequate for biomarker analysis. The local pathology report of the clear cell RCC diagnosis should be included with the sample sent to the central lab, if possible. For Cohort B, sites will submit tissues for histologic confirmation of the diagnosis of non-clear cell RCC by central histology review during the screening phase. Sites should enroll subjects in Cohort B after receiving notice that the submitted tissue was adequate for central review. Confirmation of non-clear cell RCC histology by the central laboratory will be made available to the sites as a later date. Tumor tissue collection for biomarker studies and histologic confirmation of non-clear cell RCC diagnosis should be submitted after obtaining written consent; however, tissue samples may be submitted to the central laboratory greater than 28 days prior to treatment allocation.

u. The local pathology report of the nccRCC diagnosis should be included with the sample sent to the central histology lab, if possible.

Trial Period:	**Screening**	**Treatment Cycles**												**End of Treatment**	**Post-Treatment Visits**		
		Cycles 1 to 8								Beyond Cycle 8							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of Treatment	30 days from last dose (± 3 days)	Every 6 or 12 weeks post discon (± 7 days) [a]	Every 12 weeks (± 7 days)[b]

v. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the future biomedical research (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. Blood should be collected pre-dose.

w. 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.

6.1 Second Course Phase Retreatment – (Maximum 17 Cycles)

See Section 7.1.5.2.1 for retreatment criteria.

Trial Period:	**Treatment Cycles**												**End of Treatment**	**Post-Treatment Visits**		
	Cycles 1-8								Beyond Cycle 8							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up[b]
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																
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 Anticancer Therapy Status															X	X
Survival Status[b]	<----------												---------->			X[b]
Clinical Procedures/Assessments																
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	
Full Physical Examination	X												X			
Directed Physical Examination		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				
Efficacy Measurements																
Tumor Imaging - chest, abdomen, pelvis (CAP)	X[f]														X[g]	
Tumor Imaging – bone scan	X[h]															
Tumor Imaging – brain scan	X[i]															
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																
Pregnancy Test – Urine or Serum β-HCG[j]	X															
PT/INR and aPTT	X[k]															
Hematology[l]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry[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 Visits		
	Cycles 1-8								Beyond Cycle 8							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9	10	11	12	Discon	Safety Follow-up	Efficacy Follow-up	Survival Follow-up[b]
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)
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. Second course Cycle 1 treatment must be given within 3 days of registering this visit in the IVRS.
b. The Survival Follow-up may be conducted as a telephone call or a clinic visit approximately Q12W (visit window is ± 14 days after Week 104). 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. Record all AEs and ECIs occurring within 30 days after the last dose of trial treatment regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs occurring up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Any treatment-related SAEs must be reported regardless of time they occur (see Sections 7.2.3.1 and 7.2.3.2 for further details regarding SAE and ECI reporting).
d. Height will be measured prior to retreatment.
e. Karnofsky Performance Status will be performed prior to retreatment (within 10 days prior to the first re-treatment dose of pembrolizumab), Cycles 1–8, and every 2 cycles thereafter (Cycles 10, 12, 14,…).
f. The initial tumor imaging will be performed within 28 days prior to first retreatment cycle and then every 12 weeks thereafter (84 days ±7 days).
g. In subjects who discontinue trial treatment without documented disease progression, subjects should continue with imaging assessments per the protocol defined schedule until: 1) confirmation of PD, 2) initiation of a new anti-cancer treatment, 3) withdraw of consent from trial, 4) death or 5) study conclusion or termination, whichever occurs first.
h. A bone scan will be performed within 42 days prior to first re-treatment cycle. If a subject has a positive bone scan at screening, bone scans will be performed additionally every 24 weeks thereafter (168 days ±14 days). The timing of imaging assessments should follow calendar days from allocation 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 required for subjects with brain metastasis in the Efficacy follow up phase only 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 re-treatment dose of pembrolizumab. 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 will be performed within 10 days prior to the first retreatment dose, on Day 1 of every retreatment cycle from Cycle 2 onwards, at treatment discontinuation, and at the Safety Follow-up visit.
m. Urinalysis and T3, FT4 and TSH will be performed prior to retreatment, every 2 cycles starting at Cycle 2 (Cycles 4, 6, 8,…), 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 or each subject's legally acceptable representative 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 or by the subject's legally acceptable representative'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. 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 important 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 and stage at 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 subsequent anti-cancer therapy eCRF page. If a subject initiates another anti-cancer therapy while receiving pembrolizumab, pembrolizumab must 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 allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. IVRS will be used to assign a treatment/randomization number to eligible subjects. 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.

If participants are enrolled in an extension study, participants will be assigned a new allocation number; however, each participant will retain her/her original treatment/allocation number as well.

7.1.1.9 Trial Compliance (Medication/Diet/Activity/Other)

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Sec. 5.2.2 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab.

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.

Administration of trial medication will be monitored by the investigator and/or trial staff.

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 in section 6.0 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 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs and ECIs occurring within 30 days after the last dose of trial treatment must be recorded regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs occurring up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur (see Sections 7.2.3.1 and 7.2.3.2 for further details regarding SAE and ECI reporting).

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly a potentially immunologic etiology (irAEs); see Section 5.6 regarding the identification, evaluation, and management of potential irAEs.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Examination

The investigator or clinical designee will perform a complete (full) physical exam during the Screening visit and at End of Treatment visit, 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 the first dose of trial treatment, new clinically significant abnormal findings at End of Treatment visit 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 Chart in Section 6.0. Directed physical exam (PE) refers to symptoms directed physical exam. 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 temperature, pulse, respiratory rate, and blood pressure) and weight at Screening, prior to administration of study medication at each visit as specified in the Trial Flow Chart in Section 6.0. Height will be measured at Screening only.

7.1.2.5 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at Screening and as clinically indicated throughout the trial. Clinically significant abnormal findings should be recorded in the medical history.

7.1.2.6 Karnofsky Performance Status

Karnofsky Performance Status 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 description of the full scale. The KPS will be assessed as specified in the trial Flow Chart in Section 6.0. A Karnofsky Performance Status ≥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 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 throughout the trial to optimize the visualization of existing and new tumor burden.

For both Cohorts A and B, confirmation of measurable disease by BICR per RECIST 1.1 will be used to determine eligibility prior to enrollment. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

All scheduled images for all study subjects from the sites will be submitted for BICR. Images (including other modalities) obtained to determine disease progression at unscheduled time

points must be submitted to the central imaging vendor. In addition, images obtained for other reasons but capturing radiologic progression, should be submitted for BICR.

The local site investigator/radiologist will determine disease progression for subjects in Cohort A. For subjects in Cohort B, disease progression will be verified by BICR following the first radiologic evidence of PD determined by the local site investigator/radiologist. Expedited verification of radiologic PD by BICR will be communicated to the study site and sponsor for subjects in Cohort B (see Section 7.1.2.7.6).

7.1.2.7.1 Tumor Imaging at Screening

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. For this study, imaging of the chest, abdomen, and pelvis (CAP) is required for all subjects at Screening. A subject must have measurable disease per RECIST 1.1 as assessed by investigator at baseline in order to be eligible. After measurable disease per RECIST 1.1 is determined by the site investigator/radiologist, baseline images must be submitted to the central imaging vendor for BICR verification of measurable disease. Blinded independent central imaging review confirmation of measurable disease per RECIST 1.1 is required for eligibility prior to allocation.

Bone scans will be acquired for all subjects at screening. Bone scans are not required to be repeated at screening if performed within 42 days prior to treatment allocation. Additionally, 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 for use as screening tumor imaging if they are of diagnostic quality, complete and performed within 28 days prior to the date of allocation 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 Chart (Section 6.0).

The first post allocation imaging assessment of CAP should be performed at Week 12 (84 days ±7 days) from the date of allocation. Subsequent tumor imaging of CAP should be performed Q6W (42 days ±7 days) through Week 54 and Q12W (84 days ±7 days) thereafter. 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 the allocation. All scheduled and supplemental imaging must be submitted to the central imaging vendor for BICR.

If a subject has a positive bone scan at Screening, post-allocation 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 Screening. 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. For subjects with equivocal bone lesions at baseline, bone scan should be performed in accordance with the aforementioned schedule until the lesions are determined non-cancerous.

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

For the clear cell cohort (Cohort A), when a subject is identified with PD by the site investigator/radiologist, PD will be confirmed by the site ≥ 4 weeks after the first radiologic evidence of PD (for clinically stable subjects). Subjects who are clinically stable may continue on treatment at the discretion of the investigator until progression is confirmed with a repeat scan per irRECIST. (Details pertaining to irRECIST are provided in Section 7.1.2.7.6.)

For the non-clear cell cohort (Cohort B), when a subject is identified with PD by the site investigator/radiologist, the site will submit scans to the central imaging vendor for PD verification by BICR. Subjects who are clinically stable may continue on treatment at the discretion of the investigator while awaiting verification of PD by BICR. Following PD verification by BICR, subjects who are clinically stable may continue on treatment at the discretion of the investigator until progression is confirmed at the site by a repeat scan ≥ 4 weeks after the first radiologic evidence of PD per irRECIST. (Details pertaining to irRECIST are provided in Section 7.1.2.7.6.)

Subjects who obtain a confirmation scan that does not confirm PD 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.

Additionally, for both cohorts imaging must be discontinued for initiation of new anti-cancer treatment, withdrawal of consent or study conclusion/ early termination, whichever occurs first.

7.1.2.7.3 End of Treatment and Follow-up Tumor Imaging

Subjects who discontinue trial treatment without documented disease progression, should continue tumor imaging assessments per protocol imaging schedule until initial determination of PD (or if clinically stable until further confirmation of PD), initiation of a new anti-cancer treatment, withdrawal of consent or study conclusion/early termination, whichever occurs first.

7.1.2.7.4 Second Course (Retreatment) Tumor Imaging

A subject who is eligible for the second course must have baseline imaging (performed within 28 days (CAP image) or 42 days (bone scan) prior to restarting treatment with pembrolizumab. Local reading (site investigator/radiologist assessment) will be used to determine eligibility. All second course imaging will be submitted to BICR for retrospective review.

The last imaging in initial treatment phase may also be used as the Second Course baseline imaging if it is within 28 days prior to restarting treatment and otherwise meets the baseline standards outlined in the Site Imaging Manual.

A brain scan will be performed before entering the second course for subjects with brain metastasis to ensure subject is stable. Brain imaging should be performed as clinically indicated and to confirm a CR in subjects with brain metastasis at second course baseline.

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 within 42 days prior to restarting treatment with pembrolizumab and then every Q24W thereafter (168 ± 14 days) for subjects with positive bone scan at the start of re-treatment.

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.

Subjects who discontinue treatment without confirmed disease progression should continue with imaging assessments per the protocol defined schedule until: 1) disease progression as described in Section 7.1.2.7.2, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion/early termination, whichever occurs first.

7.1.2.7.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the central imaging vendor and the investigators as the primary measure 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).

Figure 2 illustrates the imaging flow for clinically stable subjects in Cohort A. Figure 3 illustrates the imaging flow involving verification of PD for clinically stable subjects in Cohort B.

7.1.2.7.6 irRECIST Assessment of Disease

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. Immune-related RECIST 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 will be evaluated retrospectively.

When feasible, subjects should not be discontinued until progression is 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 it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management; see Table 8, Figure 2 and Figure 3). This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and 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 performance status
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 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 treatment 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 specified in Section 6 - Trial Flow Chart and be submitted to the central imaging vendor.

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

Table 8 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 (Cohort A) OR 1st radiologic evidence of PD by RECIST 1.1 which has been verified by BICR (Cohort B)	Repeat imaging ≥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

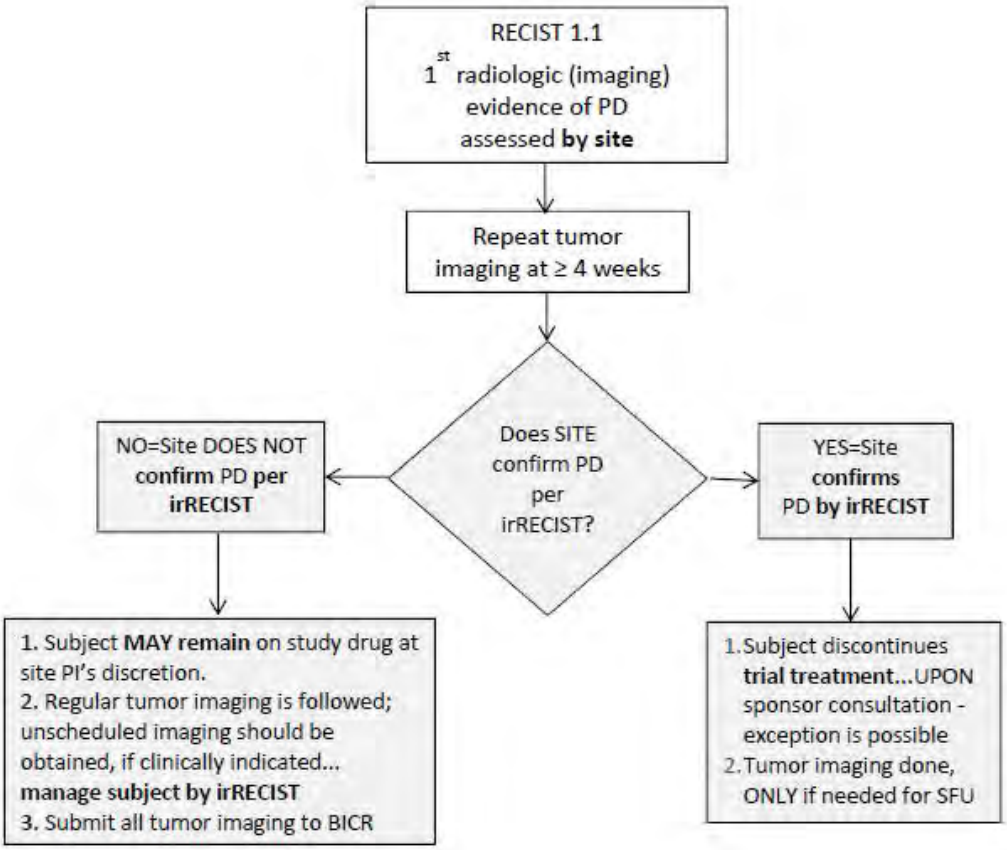


Figure 2 Imaging and Treatment for Clinically Stable Subjects in Cohort A after First Radiologic Evidence of PD Assessed by the Site

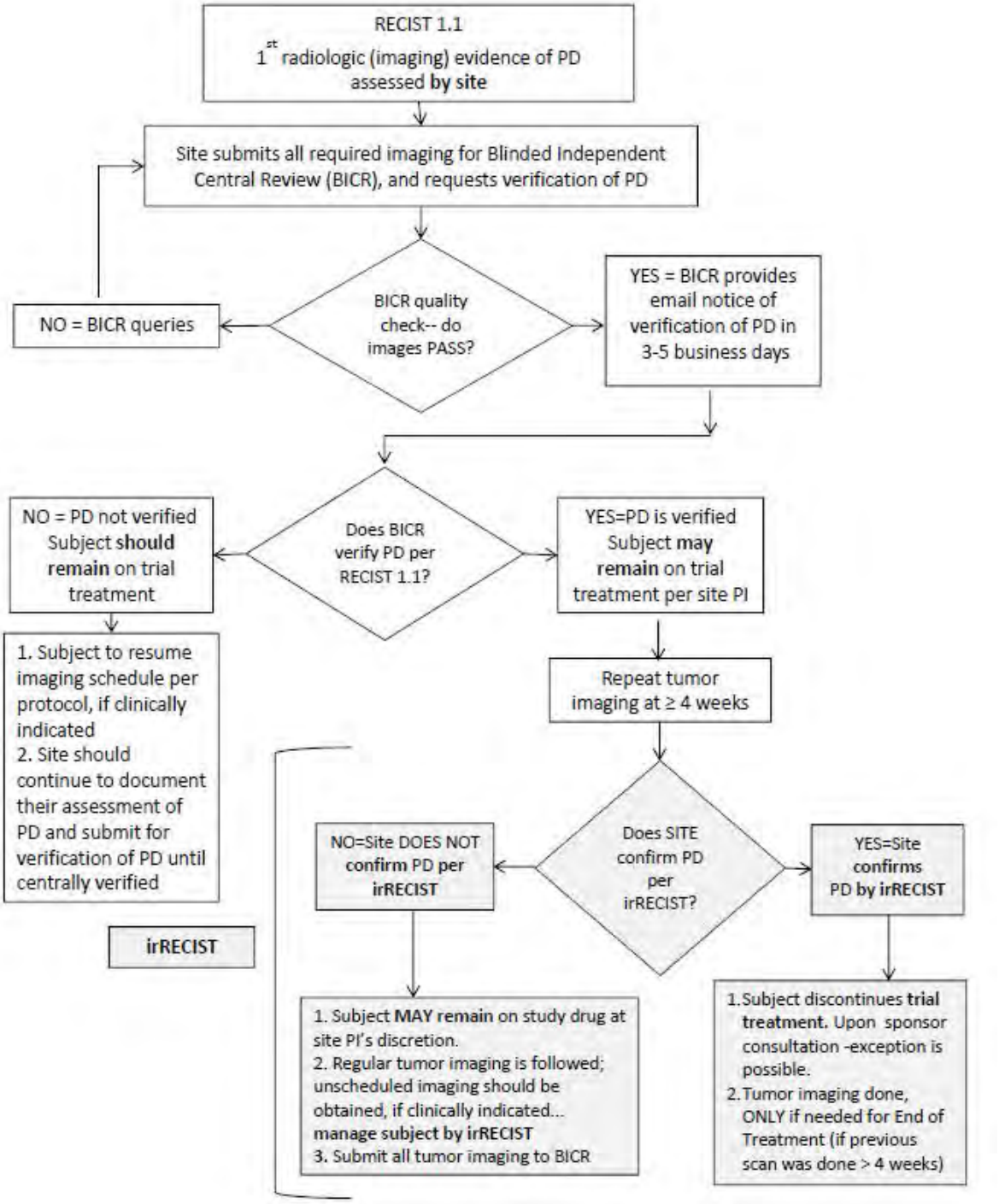


Figure 3 Imaging and Treatment for Clinically Stable Subjects in Cohort B after First Radiologic Evidence of PD Assessed by the Site

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.

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 9. The schedule of individual laboratory tests is shown in the Trial Flow Chart in Section 6.0.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum or urine pregnancy β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PTT (INR)
Platelet count	ALT	Protein	aPTT
White Blood Cells	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		
	Lactate Dehydrogenase		

Hematology	Chemistry	Urinalysis	Other
	Phosphorus or Phosphate		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal Total protein		
	Thyroid function: free thyroxine (FT3, FT4), and TSH[g]		

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 [Section 12.5]).
f. GFR (measured or calculated) or CrCl can be used in place of creatinine.
g. Free T3 may be performed in place of Total T3 per local standards

Laboratory safety tests will be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

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 test (T3, FT4, and TSH) results after dosing is acceptable.

7.1.3.2.1 Pharmacokinetic Evaluations/ Anti -pembrolizumab Antibodies

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure, samples for PK and anti-drug (pembrolizumab) antibodies (ADA) samples will be collected as specified in Trial Flow Chart -Section 6.0.

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

Additional post-dose PK samples should be drawn within 30 minutes after the end of pembrolizumab infusion at Cycles 1 and 9.

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.

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.

Sample collection, storage and shipment instructions will be provided in the Procedures Manual.

7.1.3.3 Tumor Tissue Collection

For Cohorts A and B, 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. This tissue should come from the site of metastasis, if available. Informed consent for the study must be taken prior to collection of a fresh biopsy. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR (see Section 4.2.3.4 for rationale). Details regarding time points for collection of tumor tissue are outlined in the Trial Flow Chart-Sections 6.0. For Cohort A, include a copy of the local pathology report with the tissue for biomarker analysis. For Cohort B, a copy of the local pathology report will be included with the sample collected for central histology as described below.

Fresh tissue/FFPE block/or unstained slides may be submitted for biomarker analysis (see Procedures Manual for details). Adequacy of the sample submitted for biomarker analysis must be determined by the central laboratory as a prerequisite for enrollment in both Cohort A and B.

Specimen Collection for Cohort B Central Confirmation of Non-clear Cell Histology

For Cohort B, sites will submit tissues for histologic confirmation of the diagnosis of non-clear cell RCC by central histology review during the screening phase. Sites should enroll subjects in Cohort B after receiving notice that the submitted tissue was adequate for central review. Confirmation of non-clear cell RCC histology by the central laboratory will be made available to the sites as a later date.

For confirmation of non-clear cell carcinoma, the entire case of stained slides used to determine the diagnosis must be submitted to the central laboratory. If a site cannot submit all the stained slides used for the diagnosis, then a set of H and E stained slides consisting of 1 slide cut from each block used to make the diagnosis needs to be submitted. Sites will also be required to send 1 tumor block or 7 unstained slides (in addition to the tissue sample sent for biomarker testing). This tissue will be used for IHC to be performed at the central lab. Once the laboratory has confirmed the diagnosis, the original stained slides from the case will be returned to the site. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.3.3.1 Cohort B Substudy of PD-L1 Expression in Area of Highest Furhman Grade

The collecting of the entire case allows for evaluation of tumor heterogeneity (including sarcomatoid differentiation). It has been shown that RCC tissues display significant intratumoral heterogeneity in the expression of candidate biomarkers. Therefore, in order to avoid false negative results these areas should be specifically selected for assessment. After confirmation of non-clear histology, the central laboratory will determine the area of highest Fuhrman grade in the slides that were submitted from the entire case. The central laboratory will then request that the site send unstained slides or a single tumor block from this area for further PDL-1 testing.

Submission of these additional slides or block is strongly encouraged in order to complete this important sub study. It is, however, not required for allocation to Cohort B.

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

7.1.3.4 Blood Collections for ctDNA, TCR, RNA, Plasma, and Serum

The following samples must be collected prior to dosing at the time points in accordance with the Trial Flow Chart in Section 6.0: circulating tumor DNA (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 Procedures Manual.

7.1.3.5 Planned Genetic Analysis Sample Collection

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

7.1.3.6 Future Biomedical Research Sample Collection

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

DNA for future research.

- Leftover 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 complete 35 infusions of pembrolizumab (approximately 2 years) must discontinue treatment. Subjects who attain a confirmed CR or complete 35 infusions of pembrolizumab with SD, PR or CR may have the option of restarting treatment if they experience disease progression after stopping pembrolizumab and meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following confirmation of CR or 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 Efficacy Follow-up (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 Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and 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.

Critical Equipment for this trial includes:

- Laboratory equipment- as required for inclusion labs and trial assessments

- Imaging equipment- as required for trial objectives
- Infusion equipment- as required for administering drug product.

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 that 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.

Written consent must be obtained prior to performing any protocol-specified procedures. Informed consent may be obtained greater than 28 days prior to treatment allocation; however, it MUST be obtained prior to performing any protocol-specified procedures (Section 6 – Trial Flow Chart). Tumor tissue collection for biomarker studies and histologic confirmation of non-clear cell RCC diagnosis should be submitted after obtaining written consent; however, tissue samples may be submitted to the central laboratory greater than 28 days prior to treatment allocation. This is in order for sites to gather tumor tissue samples and/or other information from the subjects. It is recommended that the tumor samples be collected and submitted for central laboratory review as soon as the informed consent is signed.

The remaining screening procedures are to be completed within 28 days prior to the first dose trial treatment, except for the following:

- Clinical laboratory tests are to be performed within 10 days prior to treatment initiation, and evaluation of KPS is to be performed within 10 days prior to treatment allocation.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Subjects may be rescreened once without sponsor consultation after initially failing to meet the inclusion/exclusion criteria. The sponsor should be consulted for approval prior to rescreening if a subject requires second rescreening. Procedures performed during the initial screening period are acceptable in lieu of repeat screening procedures if performed within the specified time frame for the individual procedures 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)

Subjects who stop pembrolizumab (MK-3475) with SD or better may be eligible for up to 17 additional doses of pembrolizumab (MK-3475) therapy if they progress after stopping MK-3745. This retreatment 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:

- Either
  - Stopped initial treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
    - Was treated for at least 8 doses with pembrolizumab (MK-3475) before discontinuing therapy
    - Received at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared

  OR

  - Subject had SD, PR or CR and stopped study treatment after completion of 35 doses (approximately 2 years) of pembrolizumab (MK-3475) treatment for reasons other than disease progression or intolerability

  AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab (MK-3475)
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab (MK-3475)
- Has a KPS of ≥70%
- Demonstrate adequate organ function as detailed in Section 5.1.2
- 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.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab (MK-3475). Treatment will be administered for up to 17 additional doses of pembrolizumab (approximately one year).

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

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 End of Treatment Visit

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 same time as 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.

Subjects who discontinue trial treatment for a reason other than disease progression will still be considered as on study and should continue with regularly scheduled assessments (also refer to section 7.1.5.3.3), including collecting subject information on the start of new anti-cancer therapy, disease progression, and death.

7.1.5.3.2 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted 30 days (± 3 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. At the safety Follow up visit all AEs that have occurred prior to the Safety Follow-Up Visit should be recorded.

Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.2.1) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first.

All AEs and ECIs occurring within 30 days after the last dose of trial treatment must be recorded regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs occurring up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur. (see Sections 7.2.3.1 and 7.2.3.2 for further details regarding SAE and ECI reporting).

7.1.5.3.3 Efficacy Follow-up Visits

Subjects who complete the protocol-required cycles of study intervention or who discontinue trial treatment without documented disease progression as described in Section 7.1.2.7.2, will begin the Efficacy Follow-up Phase and should continue with imaging assessments per the protocol defined schedule until: 1) disease progression, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion or early termination, whichever occurs first. Participants who completed all efficacy assessments must enter the Survival Follow-up Phase.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.2.1 will move from the Efficacy Follow-Up Phase to the Second Course Phase as described in Section 6.0 – Trial Flow Chart.

7.1.5.3.4 Survival Follow-up Contacts

Subject Survival Follow-up status will be assessed approximately every 12 weeks (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. Post-study treatments and the subject's response to them will also be collected. The first Survival Follow-up contact should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first Survival Follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in the Efficacy Follow-up Phase, the first Survival Follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

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).

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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 five 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.

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 infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with

severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

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 9 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).

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 Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to ensure the safeguard 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 an 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.

Table 10 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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

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 single-arm, open-label Phase II trial to evaluate the efficacy and safety of pembrolizumab as a first line treatment for advanced renal cell carcinoma (RCC).
Treatment Assignment	All subjects will receive pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W).
Analysis Populations	Efficacy: The All Subjects as Treated (ASaT) population will serve as the primary population for the analysis of efficacy data in this study. The analysis population for DOR consists of responders. Safety: All Subjects as Treated (ASaT)
Primary Endpoints	Objective response rate (ORR) per RECIST 1.1 by BCIR
Secondary Endpoints	DOR per RECIST 1.1 by BCIR; disease control rate (DCR) per RECIST 1.1 by BCIR; progression-free survival (PFS) per RECIST 1.1 by BCIR; overall survival (OS)
Statistical Methods for Key Efficacy Analyses	The estimate of ORR is the observed proportion of responses among the analysis population of corresponding cohort. The 95% CI for ORR will be calculated using an exact method based on the binomial distribution (Clopper-Pearson method).
Statistical Methods for Key Safety Analyses	Counts and percentages of subjects with AEs will be provided. Confidence intervals for the rates of types of AEs of interest will be estimated using an exact method based on the binomial distribution.

Interim Analyses	For the cohort of subjects with non-clear cell renal cell carcinoma, one interim analysis will be performed in this study. The interim analysis is summarized below. Details are provided in Section 8.7. • IA: o Timing: To be performed at the time when the 30th subject in this cohort has the opportunity to complete the 3rd scan o Testing: Futility check based on ORR for subjects with non-clear cell renal cell carcinoma
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The planned sample size is 255 subjects. The primary objectives for the study are to estimate the ORR in two cohorts of subjects with renal cell carcinoma (ccRCC and nccRCC). No power calculation is provided. The planned sample size is approximately 105 subjects in the ccRCC cohort and up to 150 subjects in the nccRCC cohorts.

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.

This trial is being conducted as an open-label study. There is no randomization in the study.

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

Objective Response Rate (ORR) – RECIST 1.1 by Blinded Central Imaging Review

ORR is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR) where responses are determined by RECIST 1.1.

8.4.1.2 Secondary

Duration of Response - RECIST 1.1 by Blinded Central Imaging Review

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 Blinded Central Imaging Review

DCR is defined as the percentage of subjects who have achieved CR, PR, or SD for at least 6 months based on assessments by the central imaging review per RECIST 1.1.

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

PFS is defined as the time from first day of study treatment to the first documented disease progression per RECIST 1.1 based on central imaging review or death due to any cause, whichever occurs first. See Section 8.6.1 for the censoring rules.

Overall Survival (OS)

OS is defined as the time from the first day of study treatment to the time of 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.

8.4.2 Safety Endpoints

Safety endpoints are described in Sections 4.2.3.2.

8.5 Analysis Population

Subjects will be entered into the trial when they are assigned a treatment number by the interactive voice response system (IVRS).

8.5.1 Efficacy Analysis Population

The All Subjects as Treated (ASaT) population will serve as the primary population for the analyses of efficacy data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders. Details on the approach to handling missing data are provided in Section 8.6.1 Statistical Methods for Efficacy Analyses.

8.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analyses of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one 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. Table 11 summarizes the key efficacy analyses.

Table 11 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
ORR per RECIST 1.1 assessed by blinded central imaging review	Observed proportion as point estimate and 95% CI using Clopper-Pearson method based on binomial distribution	ASaT	Subjects with missing data are considered non-responders
DOR per RECIST 1.1 assessed by blinded central imaging review	Summary statistics using Kaplan-Meier method	All responders	Details are provided in a separate table
DCR per RECIST 1.1 assessed by blinded central imaging review	Observed proportion as point estimate and 95% CI using Clopper-Pearson method based on binomial distribution	ASaT	Subjects with missing data are considered disease not under control
PFS per RECIST 1.1 assessed by blinded central imaging review	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment date
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last date the subject was known to be alive

Table 12 provides the censoring rules for DOR.

Table 12 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 after ≥ 2 missed adequate disease assessments	Last adequate disease assessment prior to the after ≥ 2 missed adequate disease assessments	Censor (Non-event)
Death or progression after ≤ 1 missed adequate disease assessments	PD or death	End of response (Event)
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		

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Counts and percentages of subjects with AEs will be provided. Confidence intervals for the rates of a list of pre-defined AEs of special interest (AEOSI) for the pembrolizumab development program will be estimated using an exact method based on the binomial distribution.

8.6.3 Summaries of Demographic and Baseline Characteristics

The number and percentage of subjects screened and enrolled and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by cohort either by descriptive statistics or categorical tables.

8.7 Interim Analyses

An interim analysis will be performed for the cohort of subjects with non-clear cell renal cell carcinoma at the time when 30th subject in this cohort has the opportunity to complete the 3rd scan. Analysis will include all scans up to this cut-off time point. A futility check will be conducted based on an observed ORR and futility will be considered if 1 or fewer responders are observed. During the futility analysis the enrollment of subjects will continue.

8.8 Multiplicity

The primary objectives for the study are to estimate the ORR in two separate cohorts of subjects with renal cell carcinoma. Therefore, no multiplicity will be considered.

8.9 Sample Size and Power Calculations

The primary objectives for the study are to estimate the ORR in two cohorts of subjects with renal cell carcinoma (ccRCC and nccRCC). The overall sample size selection is based on the confidence interval (CI) width that will provide the appropriate level of precision needed for estimation. The planned sample size is approximately 105 subjects in ccRCC cohort and up to 150 subjects in nccRCC cohort. With the above sample sizes, the 95% confidence intervals for different observed response rates are listed below with the width of the 95% confidence level. With a sample size of 105 subjects with clear cell renal cell carcinoma, the half-width of 95% confidence interval varies between 8% and 10% when the observed response rates vary from 20% to 60%. With a sample size of 150 subjects with non-clear cell renal cell carcinoma, the half-width of 95% confidence interval varies between 4% and 8% when the observed response rates vary from 5% to 30%. No power calculation is provided.

Sample size	Number of Subjects with a response	Observed Response Rate	95% CI	95% CI width
105 (ccRCC)	21	20%	(12.8%, 28.9%)	16.1%
	32	~30%	(21.9%, 40.2%)	18.4%
	42	40%	(30.6%, 50%)	19.5%
	53	~50%	(40.6%, 60.4%)	19.8%
	63	60%	(50%, 69.4%)	19.5%
150 (nccRCC)	8	~5%	(2.3%, 10.2%)	7.9%
	15	10%	(5.7%, 16%)	10.3%
	23	~15%	(9.9%, 22.1%)	12.1%
	30	20%	(13.9%, 27.3%)	13.4%
	38	~25%	(18.6%, 33%)	14.5%
	45	30%	(22.8%, 38%)	15.2%

8.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of treatment effect (with a nominal 95% CI) for the efficacy endpoints stated in Section 8.4.1 will be performed within each of IMDC risk categories (See Section 12.5).

The estimate of treatment effect (with a nominal 95% confidence interval [CI]) for the primary endpoints will be performed within each category of the following classification variables.

- Geographic region
- PD-L1 status
- Age
- Sex
- Race

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 13.

Table 13 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 25 mg/mL (100 mg/4mL)	Solution for injection	Provided centrally by the Sponsor.

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.

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.

11.0 LIST OF REFERENCES

[1] Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009 Dec 1;27(34):5794-9.

[2] Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013 Feb;14(2):141-8.

[3] Ko JJ, Xie W, Kroeger N, Lee JL, Rini BI, Knox JJ, et al. The international metastatic renal cell carcinoma database consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol. 2015 Mar;16(3):293-300.

[4] Escudier B, Porta C, Schmidinger M, Algaba F, Patard JJ, Khoo V, et al. ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii49-56.

[5] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277-300.

[6] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 2.2016. Fort Washington, PA: National Comprehensive Cancer Network (NCCN); 2015.

[7] U.S. Prescribing Information: OPDIVO (nivolumab) injection, for intravenous use: 2014.

[8] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):115-24.

[9] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S. et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009 Aug 1;27(22):3584-90.

[10] Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010 Feb 20;28(6):1061-8.

[11] Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH. et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer. 2013 Apr;49(6):1287-96.

[12] Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103-11.

[13] Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): Final analysis of overall survival. J Clin Oncol 2010;28(13):2144-50.

[14] Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013 Aug 22;369(8):722-31.

[15] Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol. 2013 Dec;14(13):1287-94.

[16] Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007 May 31;356(22):2271-81.

[17] Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009 Jul 10;27(20):3312-8.

[18] Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S. et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010 Sep 15;116(18):4256-65.

[19] U.S. Prescribing Information: AFINITOR (everolimus) tablets for oral administration, AFINITOR DISPERZ (everolimus tablets for oral suspension): 2015.

[20] Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011 Dec 3;378(9807):1931-9.

[21] Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol. 2013 May;14(6):552-62.

[22] U.S. Prescribing Information: INLYTA (axitinib) tablets for oral administration: 2012.

[23] European Medicines Agency. Committee for Medicinal Products for Human use (CHMP): CHMP assessment report: Inlyta (EMA/CHMP/453325/2012) [Internet]. London: European Medicines Agency; 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002406/WC500132190.pdf

[24] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.

[25] Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1814-23.

[26] U.S. Prescribing Information: COMETRIQ (cabozantinib) capsules, for oral use: 2012.

[27] Dutcher JP, de Souza P, McDermott D, Figlin RA, Berkenblit A, Thiele A, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. Med Oncol. 2009;26(2):202-9.

[28] Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol. 2016 Jan 12. [Epub ahead of print].

[29] Ravaud A, Oudard S, De Fromont M, Chevreau C, Gravis G, Zanetta S, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG). Ann Oncol. 2015 Jun;26(6):1123-8.

[30] Gordon MS, Hussey M, Nagle RB, Lara PN Jr, Mack PC, Dutcher J, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. J Clin Oncol. 2009 Dec 1;27(34):5788-93.

[31] Stadler WM, Figlin RA, McDermott DF, Dutcher JP, Knox JJ, Miller WH Jr, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. Cancer. 2010 Mar 1;116(5):1272-80.

[32] Irshad T, Olencki T, Zynger DL, Coston A, Mortazavi A, Monk JP. Bevacizumab in metastatic papillary renal cell carcinoma [abstract]. J Clin Oncol. 2011 May 20; 29(15 Suppl). Abstract no. e15158.

[33] Finn OJ. Molecular origins of cancer: cancer immunology. N Engl J Med. 2008 Jun 19;358(25):2704-15.

[34] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011 Mar 25;331(6024):1565-70.

[35] Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol. 2011;29:235-71.

[36] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

[37] Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol. 2013 Apr;13(4):227-42. Erratum in: Nat Rev Immunol. 2013 Jul;13(7):542.

[38] Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. Clin Immunol. 2014 Jul;153(1):145-52.

[39] Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Immunology 2008;8:467-77.

[40] Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480-9.

[41] Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012;24:207-12.

[42] Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol. 2015 Jan 20. [Epub ahead of print].

[43] Dizon DS, Krilov L, Cohen E, Gangadhar T, Ganz PA, Hensing TA. et al. Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. J Clin Oncol. 2016 Feb 4. [Epub ahead of print].

[44] U.S. Prescribing Information: KEYTRUDA (pembrolizumab) injection, for Intravenous Use: 2015.

[45] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med 2013;369(2):134-44.

[46] Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014 Sep 20;384(9948):1109-17.

[47] Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015 Aug;16(8):908-18.

[48] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015 Apr 19. [Epub ahead of print]

[49] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Apr 19.

[50] Muro K, Bang Y, Shankaran V, Geva R, Catenacci DVT, Gupta S, et al. A phase 1b study of pembrolizumab (pembro; mk-3475) in patients (pts) with advanced gastric cancer [abstract]. Ann Oncol.2014;25 Suppl 5:v1-v41.

[51] Plimack ER, Bellmunt J, Gupta S, Berger R, Montgomery RB, Heath K, et al. Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012 [abstract]. Abstracts of the 2015 ASCO Annual Meeting; 2015 May 29 to June 2; Chicago, IL. American Society of Clinical Oncology(ASCO); 2015.

[52] Seiwert TY, Burtness B, Weiss J, Gluck I, Eder JP, Pai SI, et al. A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV–associated head and neck (H/N) cancer [abstract 6011]. 2014 ASCO Annual Meeting on Clinical Science Symposium, Immunobiology and Immunotherapy; 2014.

[53] Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, et al. A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer. San Antonio Breast Cancer Symposium 2014; abstract S1-09.

[54] Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood. 2009 Aug 20;114(8):1537-44.

[55] Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.

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.

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. 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.

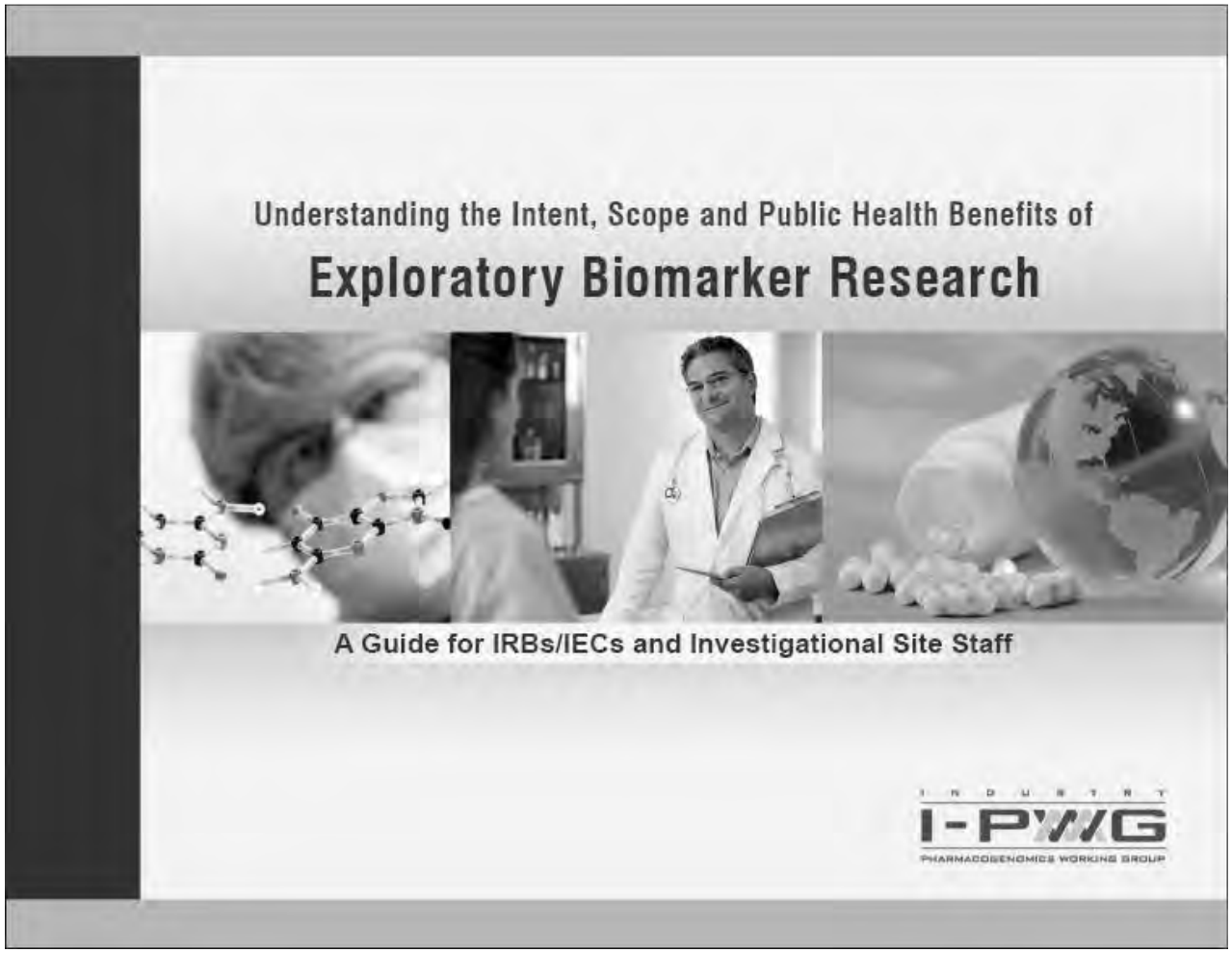
12. Questions

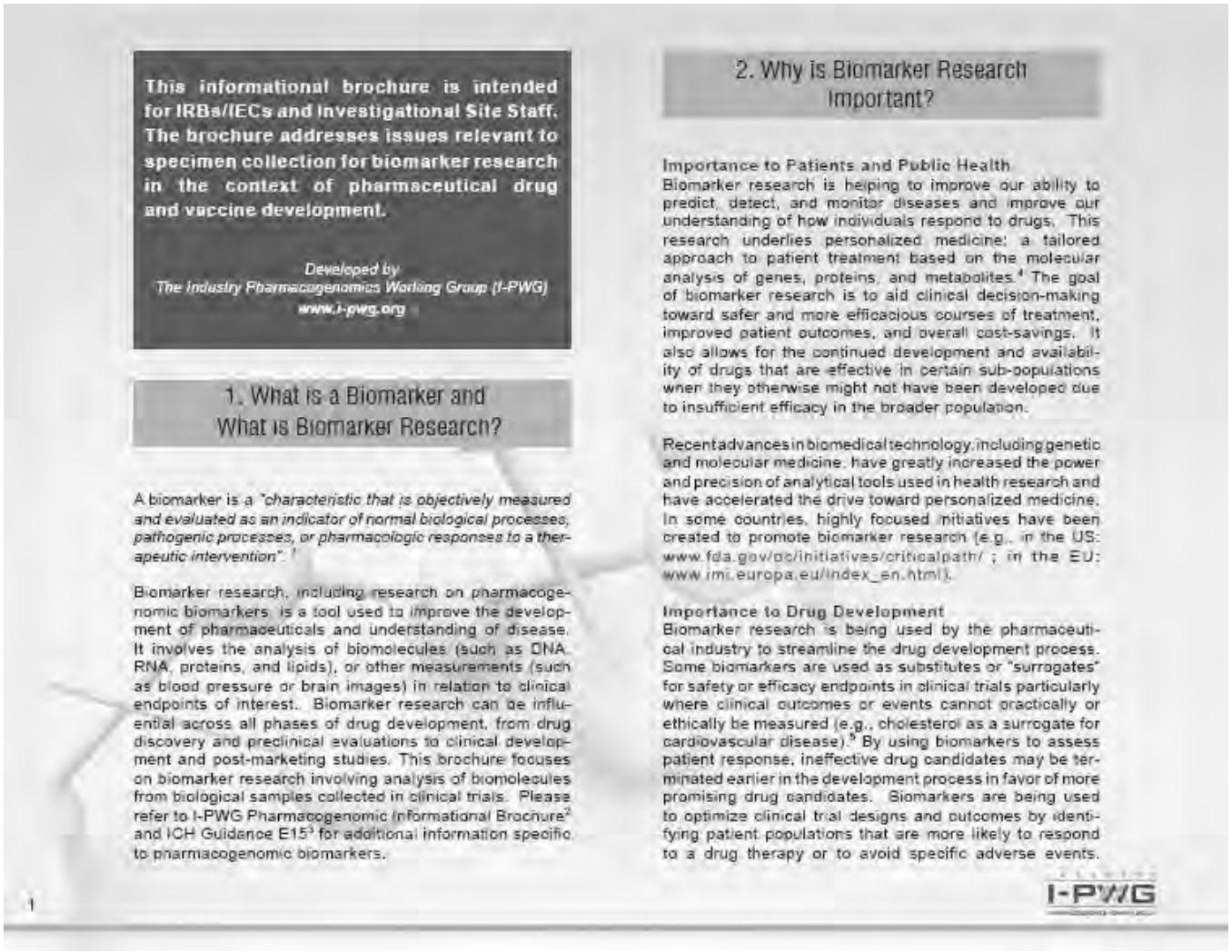
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
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

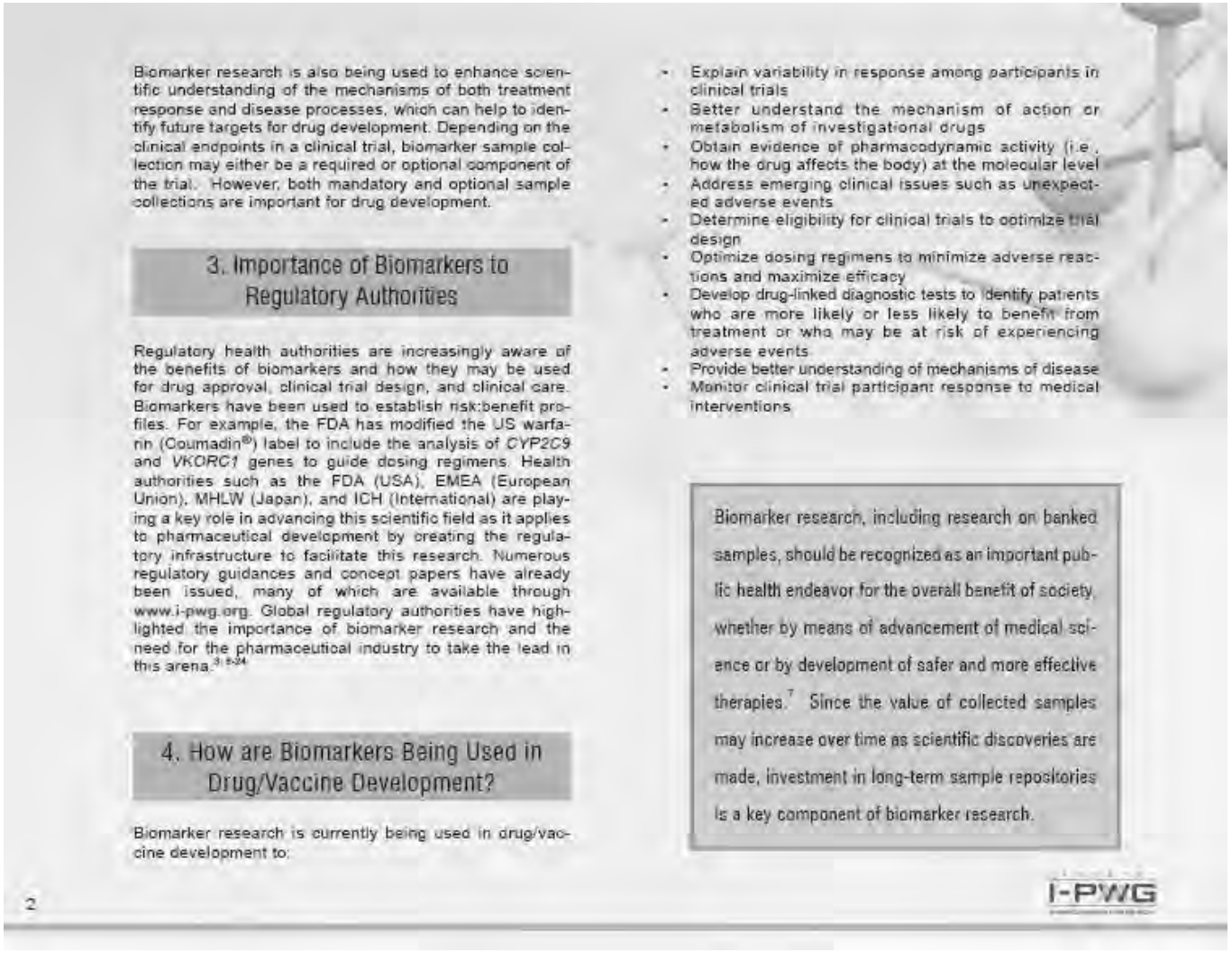
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, 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.

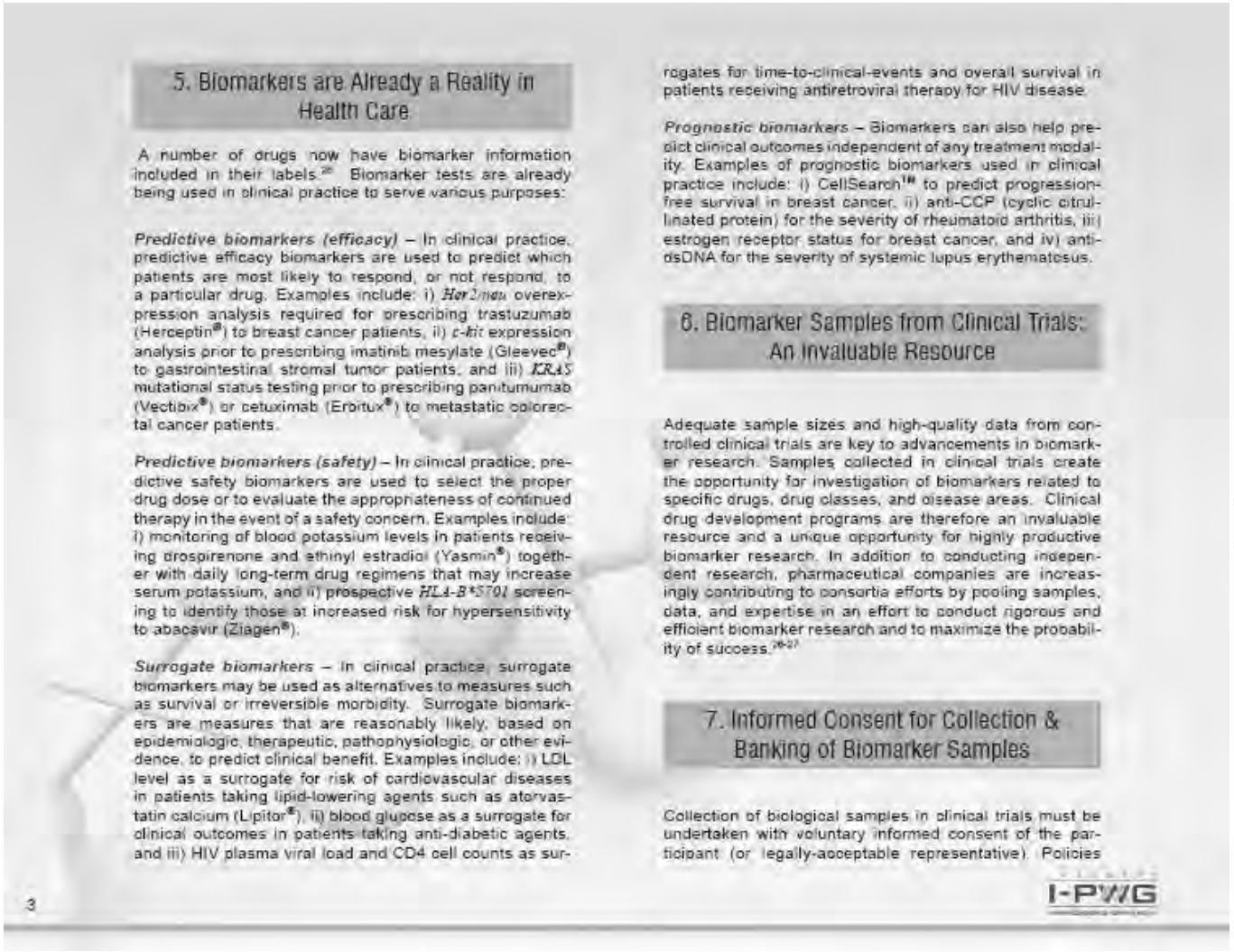
Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to 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.

I-PWG


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.[3,8-24]
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.
I-PWG
2



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

I-PWG

3

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.[29-31]

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

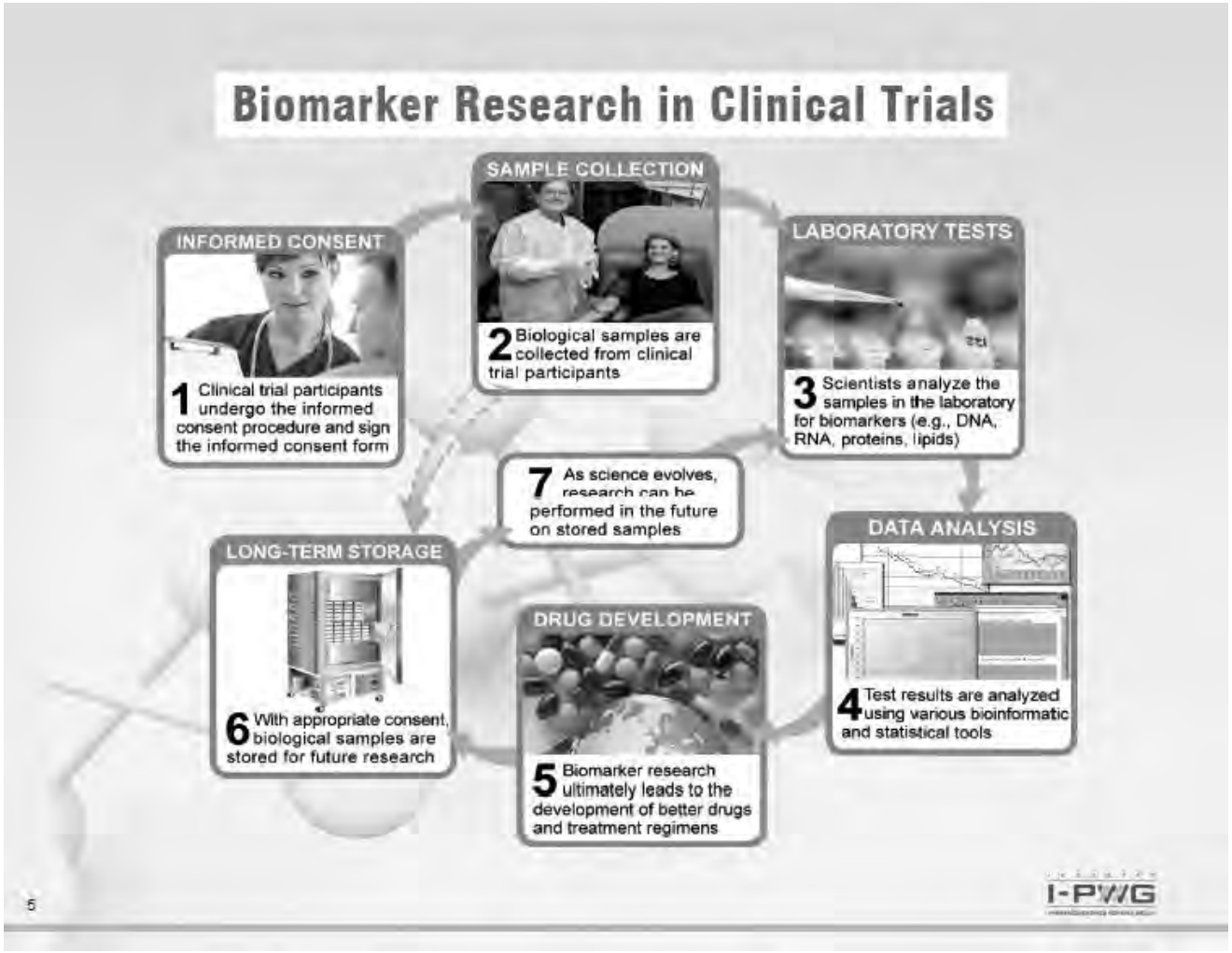
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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.[9, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

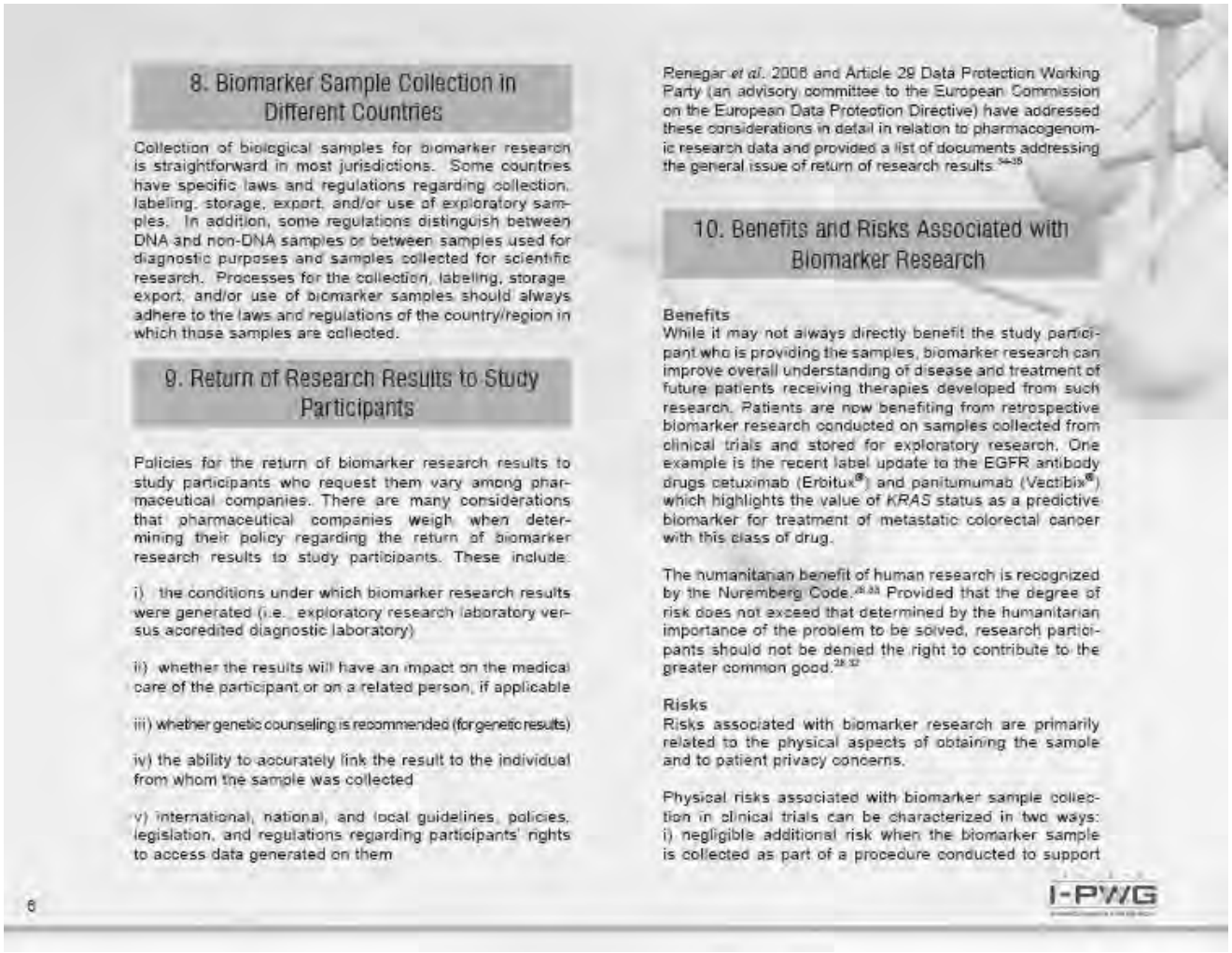
Important elements of informed consent for **future use** of samples include, but are not limited to:[29]

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.[9] 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.[31]

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.


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



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.* 2008 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.[34-38]

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.[31,33] 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

6

I-PWG

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."* [21]

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?

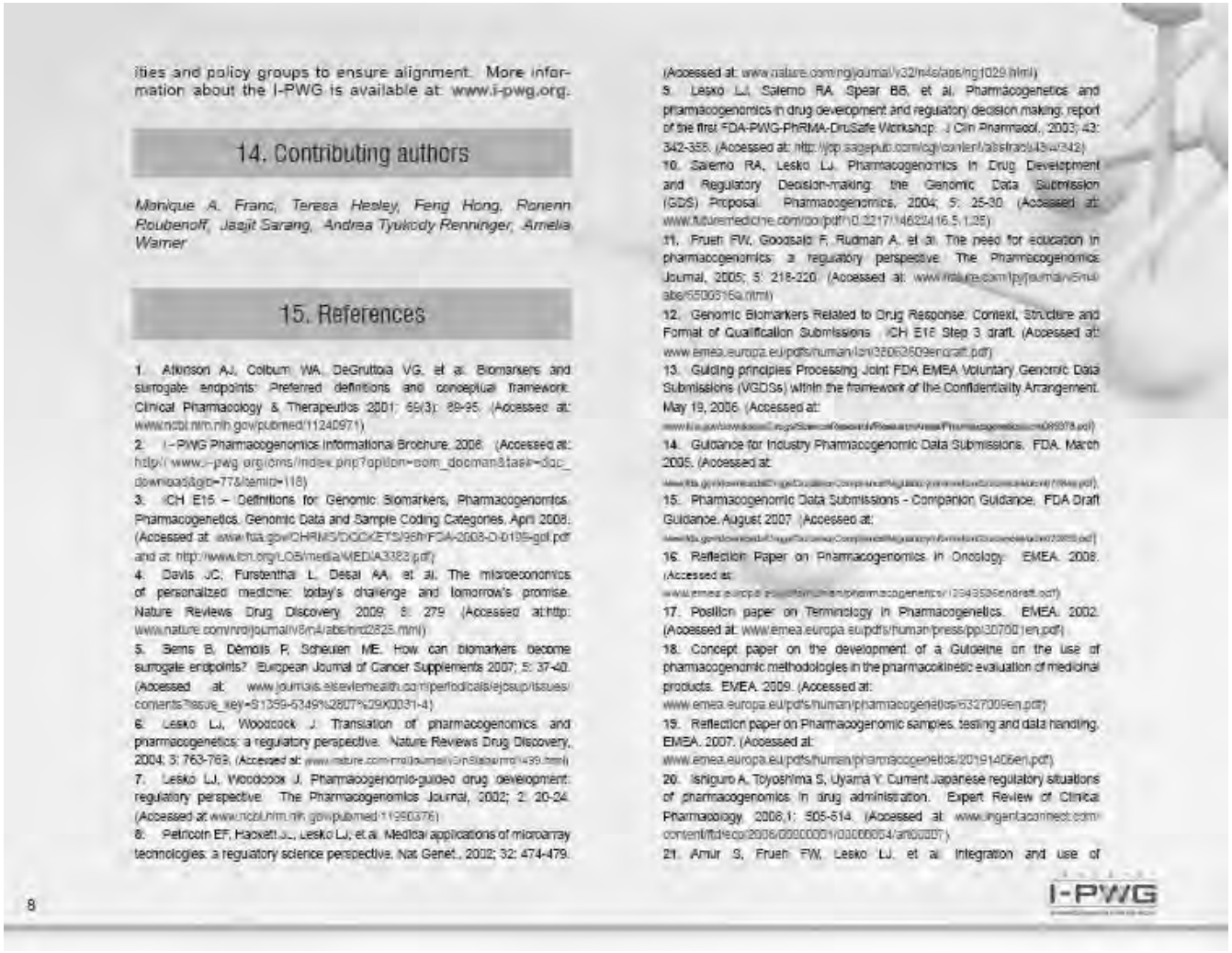
Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

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-

7

I-PWG



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, Jaajit Sarang, Andrea Tyukody Renninger, Amelia Warner

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)

2. I-PWG Pharmacogenomics Informational Brochure. 2006. (Accessed at: http://www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)

3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2006. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2006-D-0195-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)

4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery 2009; 8: 279. (Accessed at:http://www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)

5. Sems B, Dimois F, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)

6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)

7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)

8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1028.html)

9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)

10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.1517/14622416.5.1.25)

11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)

12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/3206309enrdraft.pdf)

13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at:

14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at:

15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at:

16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at:

17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/30700?en.pdf)

18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at:
www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)

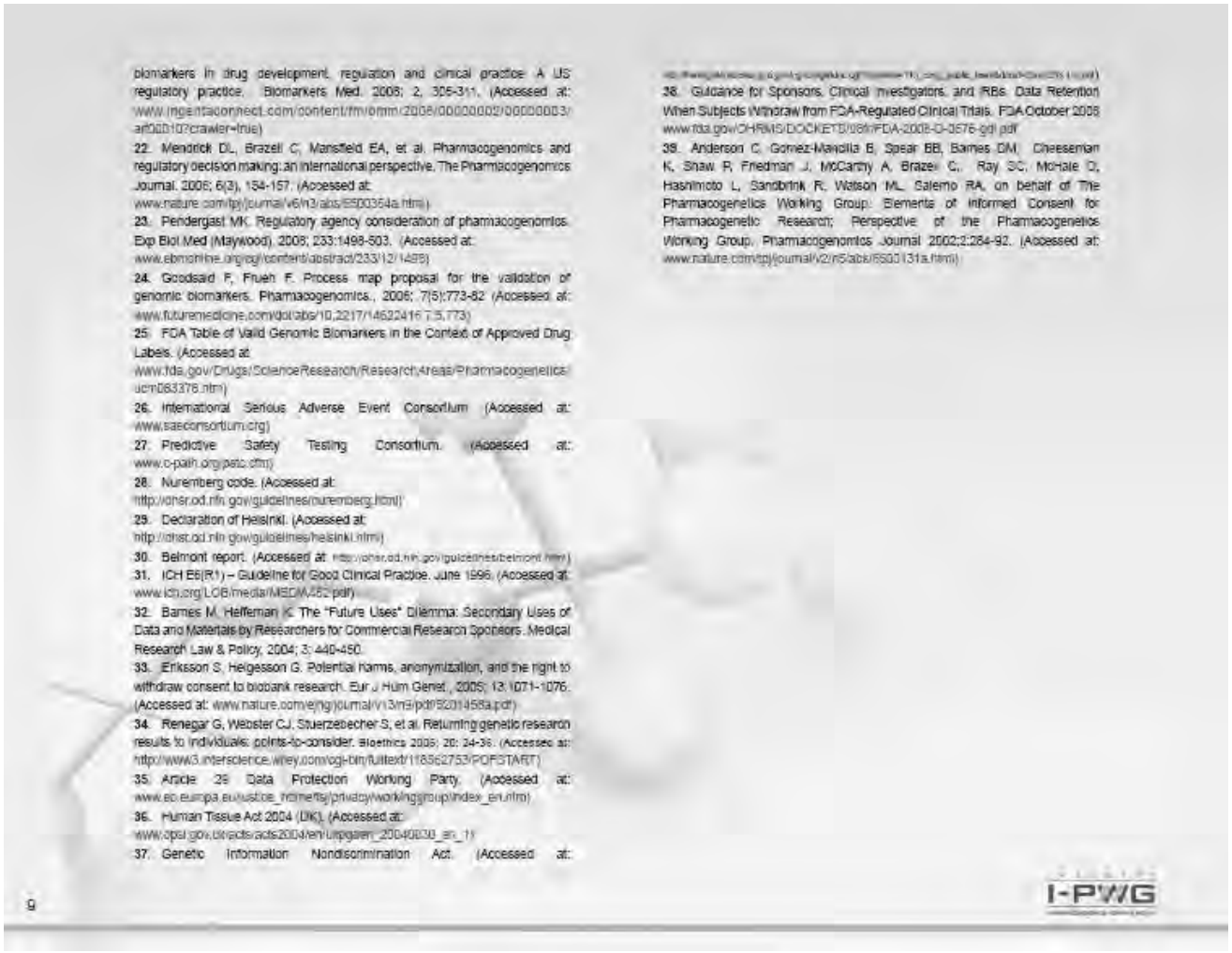
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at:
www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology. 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftl/ecp/2008/00000001/00000004/art00007)

21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

I-PWG



biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/omm/2008/00000002/00000003/art00010?crawler=true)
22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500354a.html)
23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)
24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)
25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/Research/Areas/Pharmacogenetics/ucm083376.htm)
26. International Serious Adverse Event Consortium (Accessed at: www.saeconsortium.org)
27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)
28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)
29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)
30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)
31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MEDIA482.pdf)
32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.
33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)
34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2005; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)
35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)
36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)
37. Genetic Information Nondiscrimination Act. (Accessed at:
38. Guidance for Sponsors, Clinical Investigators, and IRBs. Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf
39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw R, Friedman J, McCarthy A, Brazeau C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research: Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)

9

I-PWG


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 IMDC Risk Evaluation

Assessments	Risk Factor
Baseline Karnofsky Performance Status	< 80%
Interval between initial diagnosis of RCC to start of first-line treatment for advanced disease (*note for this study, date of allocation will be used as the start of first-line treatment*)	< 1year
Baseline Hemoglobin	< Lower limit of normal
Baseline Platelet Count	> Upper limit of normal
Baseline Corrected Calcium	> 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

12.6 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

NCI CTCAE version 4.0 will be utilized for adverse events reporting (http://ctep.cancer.gov/reporting/ctc.html)

12.7 Abbreviations

Abbreviation	Definition
ADA	anti-drug (pembrolizumab) antibodies
AE	adverse event
ALT	alanine aminotransferase
APC	antigen-presenting cells
aPTT	activated partial thromboplastic time
ASaT	all subjects as treated
AST	aspartate aminotransferase
BICR	blinded independent central imaging review/reviewer
BCG	Bacillus Calmette-Guerin
β-hCG	β human chorionic gonadotropin
BID	*bis in die* (twice a day)
CAP	chest, abdomen, and pelvis
cc	clear-cell
ccRCC	clear-cell renal cell carcinoma
CI	confidence interval
CIV	central imaging vendor
CL	clearance
CNS	central nervous system
CR	complete response
CrCl	calculated creatinine clearance
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTL	cytotoxic T lymphocytes cells
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
e.g.	*exempli gratia* (for example)
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ERC	Ethical Review Committee ()
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
FT3, FT4	free thyroxine
GI	gastrointestinal
GFR	glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
i.e.	*id est* (that is)
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Definition
IFNα	interferon alpha
IHC	immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
INR	International normalized ratio
irAEs	immune-related adverse events
IRB	Institutional Review Board
irRECIST	immune-related RECIST
IV	intravenous
IVRS	interactive voice response system
KPS	Karnofsky Performance Status
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
ncc	non-clear cell
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/PD-L2	programmed death-ligand 1/2
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os (by mouth)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
QD	*quaque die* (once a day)
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results [Program]
sSAP	statistical analysis plan
T3	total triiodothyronine
T4	thyroxine
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
W	week(s)
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	

Supplemental Statistical Analysis Plan (sSAP)

TABLE OF CONTENTS

LISTING OF TABLES

C Confidential

1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization. There will be a separate PK analysis plan as well as biomarker analysis plan.

2 SUMMARY OF CHANGES

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
3.3	Hypotheses/Estimation	Add "All estimation will be applied on the ccRCC (cohort A) and nccRCC (cohort B) separately. For nccRCC (cohort B), two sets of analyses will be performed due to additional diagnosis confirmation of nccRCC by blinded central histology review. • Primary analysis will be on the subjects in cohort B who had confirmation of nccRCC diagnosis by blinded central histology review • Sensitivity analysis will be on all subjects in cohort B by consultative review."	To clarify the cohort B nccRCC population definition
3.6.1	Statistical Methods for Efficacy Analyses	• Updated the table for	• To align with the updated oncology

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
		censoring rules for DOR • Added a table to provide the censoring rules for PFS	standard censoring rules for DOR. • To align with the oncology standard primary censoring rules for PFS.
3.6.2	Statistical Methods for Safety Analyses	Removed analysis of AEOSIs by confidence intervals. Only count and percentage will be provided.	To align with standard analysis of AEOSIs. No need to provide confidence intervals.
3.10	Subgroup Analyses and Effect of Baseline Factors	Addition of subgroup analysis by IMDC category 2 of favorable vs intermediate/poor.	IMCD favorable vs. intermediate/poor is a clinically meaning breakdown that has been commonly presented in the literature.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2-3.12.

Study Design Overview	This is a single-arm, open-label Phase II trial to evaluate the efficacy and safety of pembrolizumab as a first line treatment for advanced renal cell carcinoma (RCC).
Treatment Assignment	All subjects will receive pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W).
Analysis Populations	Efficacy: The All Subjects as Treated (ASaT) population will serve as the primary population for the analysis of efficacy data in this study. The analysis population for DOR consists of responders. Safety: All Subjects as Treated (ASaT)
Primary Endpoints	Objective response rate (ORR) per RECIST 1.1 by BCIR
Secondary Endpoints	Duration of response (DOR) per RECIST 1.1 by BCIR; disease control rate (DCR) per RECIST 1.1 by BCIR; progression-free survival (PFS) per RECIST
Statistical Methods for Key Efficacy Analyses	The estimate of ORR is the observed proportion of responses among the analysis population of corresponding cohort. The 95% CI for ORR will be calculated using an exact method based on the binomial distribution (Clopper- Pearson method).
Statistical Methods for Key Safety Analyses	Counts and percentages of subjects with AEs will be provided. Confidence intervals for the rates of types of AEs of interest will be estimated using an exact method based on the binomial distribution.

Study Design Overview	This is a single-arm, open-label Phase II trial to evaluate the efficacy and safety of pembrolizumab as a first line treatment for advanced renal cell carcinoma (RCC).
Interim Analyses	For the cohort of subjects with non-clear cell renal cell carcinoma, one interim analysis will be performed in this study. The interim analysis is summarized below. Details are provided in Section 3.7. • IA: o Timing: To be performed at the time when 30th subject in this cohort has the opportunity to complete the 3rd scan o Analysis: Futility check based on ORR for subjects with non-clear cell renal cell carcinoma
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The planned sample size is 255 subjects. The primary objectives for the study are to estimate the ORR in two cohorts of subjects with renal cell carcinoma (ccRCC and nccRCC). No power calculation is provided. The planned sample size is approximately 105 subjects in the ccRCC cohort and up to 150 subjects in the nccRCC cohorts.

3.2 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.

This trial is being conducted as an open-label study. There is no randomization in the study.

3.3 Hypotheses/Estimation

There will be no formal hypothesis testing in this study. Objectives of the study are stated in the Protocol Section 3.0.

All estimation will be applied on the ccRCC (cohort A) and nccRCC (cohort B) separately. For nccRCC (cohort B), two sets of analyses will be performed due to additional diagnosis confirmation of nccRCC by blinded central histology review in addition to the consultative review.

- Primary analysis will be on the subjects in cohort B who had confirmation of nccRCC diagnosis by blinded central histology review
- Sensitivity analysis will be on all subjects in cohort B by consultative review.

3.4 Analysis Endpoints

3.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

3.4.1.1 Primary

Objective Response Rate (ORR) – RECIST 1.1 by Blinded Independent Central Review (BICR)

ORR is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR) where responses are determined by RECIST 1.1.

3.4.1.2 Secondary

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 3.6.1 for the censoring rules.

Disease Control Rate (DCR) - RECIST 1.1 by BICR

DCR is defined as the percentage of subjects who have achieved CR, PR, or stable disease (SD) for at least 6 months based on assessments by the central imaging review per RECIST 1.1.

Progression-Free Survival (PFS) – RECIST 1.1 by BICR

PFS is defined as the time from first day of study treatment to the first documented disease progression per RECIST 1.1 based on central imaging review or death due to any cause, whichever occurs first. See Section 3.6.1 for the censoring rules.

Overall Survival (OS)

OS is defined as the time from the first day of study treatment to the time of 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.

3.4.1.3 Exploratory

Exploratory endpoints of this study include ORR, DOR, DCR and PFS per irRECIST by BICR and PK parameter.

3.4.2 Safety Endpoints

The safety objective is to characterize the safety and tolerability of pembrolizumab in subjects with advanced RCC as first line treatment. The following safety parameters will be analyzed: adverse events and serious adverse events graded per National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (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 of use. These are routine safety parameters collected and analyzed in Phase II oncology trials. Furthermore, specific immune-related adverse events (irAEs) will be collected.

3.5 Analysis Populations

Subjects will be entered into the trial when they are assigned a treatment allocation number by the IVRS.

3.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will serve as the primary population for the analyses of efficacy data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders. Details on the approach to handling missing data are provided in Section 3.6.1 Statistical Methods for Efficacy Analyses.

3.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analyses of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one 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.

3.6 Statistical Methods

3.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. These methods will also be applied to the exploratory endpoints of ORR, DOR, DCR, PFS per irRECIST by BICR. .

Table 1 summarizes the key efficacy analyses.

Table 1 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
ORR per RECIST 1.1 assessed by blinded central imaging review	Observed proportion as point estimate and 95% CI using Clopper-Pearson method based on binomial distribution	ASaT	Subjects with missing data are considered non- responders
DOR per RECIST 1.1 assessed by blinded central imaging review	Summary statistics using Kaplan-Meier method	All responders	Details are provided in a separate table
DCR per RECIST 1.1 assessed by blinded central imaging review	Observed proportion as point estimate and 95% CI using Clopper-Pearson method based on binomial distribution	ASaT	Subjects with missing data are considered disease not under control
PFS per RECIST 1.1 assessed by blinded central imaging review	Summary statistics using Kaplan-Meier method	ASaT	Details are provided in a separate table
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last date the subject was known to be alive

Table 2 provides the censoring rules for DOR. Table 3 provides the censoring rules for PFS.

Table 2 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 consecutively 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 adequate 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.		

Table 3 Censoring Rules for PFS

Situation	**Outcome**
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
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
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment

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

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Counts and percentages of subjects with AEs and AEs of special interest (AEOSI) will be provided.

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened and enrolled and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by cohort either by descriptive statistics or categorical tables.

The following analyses will be performed by cohort: DOR, DCR and PFS per RECIST 1.1 by BICR and OS (with a nominal 95% confidence interval [CI]) will be estimated by centrally determined PD-L1 status as well as for patients with any sarcomatoid differentiation identified.

3.7 Interim Analyses

An interim analysis will be performed for the cohort of subjects with non-clear cell renal cell carcinoma at the time when 30th subject in this cohort has the opportunity to complete the 3rd scan. Analysis will include all scans up to this cut-off time point. A futility check will be conducted based on an observed ORR and futility will be considered if 1 or fewer responders are observed. During the futility analysis the enrollment of subjects will continue.

3.8 Multiplicity

The primary objectives for the study are to estimate the ORR in two separate cohorts of subjects with renal cell carcinoma. Therefore, no multiplicity will be considered.

3.9 Sample Size and Power Calculations

The primary objectives for the study are to estimate the ORR in two cohorts of subjects with renal cell carcinoma (ccRCC and nccRCC). The overall sample size selection is based on the confidence interval (CI) width that will provide the appropriate level of precision needed for estimation The planned sample size is approximately 105 subjects in ccRCC cohort and up to 150 subjects in nccRCC cohort. With the above sample sizes, the 95% confidence intervals for different observed response rates are listed below with the width of the 95% confidence level. With a sample size of 105 subjects with clear cell renal cell carcinoma, the half-width of 95% confidence interval varies between 8% and 10% when the observed response rates vary from 20% to 60%. With a sample size of 150 subjects with non-clear cell renal cell carcinoma, the half-width of 95% confidence interval varies between 4% and 8% when the observed response rates vary from 5% to 30%. No power calculation is provided.

Sample size	Number of Subjects with a response	Observed Response Rate	95% CI	95% CI width
105 (ccRCC)	21	20%	(12.8%, 28.9%)	16.1%
	32	~30%	(21.9%, 40.2%)	18.4%
	42	40%	(30.6%, 50%)	19.5%
	53	~50%	(40.6%, 60.4%)	19.8%
	63	60%	(50%, 69.4%)	19.5%
150 (nccRCC)	8	~5%	(2.3%, 10.2%)	7.9%
	15	10%	(5.7%, 16%)	10.3%
	23	~15%	(9.9%, 22.1%)	12.1%
	30	20%	(13.9%, 27.3%)	13.4%
	38	~25%	(18.6%, 33%)	14.5%
	45	30%	(22.8%, 38%)	15.2%

3.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of treatment effect (with a nominal 95% CI) for the efficacy endpoints stated in Section 3.4.1 will be performed within each of IMDC risk categories (favorable, intermediate, and poor) as well as within IMDC risk categories of favorable and a combined intermediate and poor category (See Protocol Appendix 12.5).

The estimate of treatment effect (with a nominal 95% confidence interval [CI]) for the primary endpoints will be performed within each category of the following classification variables.

- Geographic region
- PD-L1 status
- Age
- Sex
- Race

3.11 Compliance (Medication Adherence)

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

3.12 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.

REVISION HISTORY

Date	Summary of Change
11AUG2016	Original Document
27JUL2017	Clarification of Cohort B population
29AUG2018	Updated DOR censoring rules, added PFS censoring rules, removed CIs for AEs and AEOSI, and added IMDC category 2