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TITLE:

A Clinical Trial to Evaluate the Effect of Neoadjuvant MK-3475 (Pembrolizumab) Therapy on Intratumoral Immune Infiltrates in Renal Cell Cancer (RCC) Patients Undergoing Surgical Resection

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2/5.2.1.2.1.2	Dose Modification and toxicity Management Guidelines for Pembrolizumab/Post-Resection MK-3475	Replaced the Dose Modification Guidelines Table. Table now includes added guidelines for dose modification in the event of myocarditis and updated guidelines for several other conditions.	To align with the most current label and safety information for pembrolizumab.
5.6.2	Supportive Care Guidelines During Post-Resection MK-3475 Treatment for this Trial	Updated the risk language and replaced the Infusion Reaction Treatment Guidelines Table.	To align with the most current safety information for pembrolizumab

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Neoadjuvant MK-3475 (pembrolizumab) RCC Study
Trial Phase	Phase I
Clinical Indication	Neoadjuvant treatment of RCC (≥T1b)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Neoadjuvant MK-3475, then standard-of-care (SOC) surgical RCC resection vs. No neoadjuvant therapy, with SOC surgical RCC resection; Followed by post-resection MK-3475 for all subjects.
Number of trial subjects	Approximately 36 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	After a screening phase of 1-2 weeks, each subject assigned neoadjuvant MK-3475 will receive 2 (possibly 3) Q3 week cycles of treatment followed by surgical RCC resection, while subjects not assigned to neoadjuvant treatment will proceed directly to RCC resection. Following recovery from surgery, all subjects will receive MK-3475 Q3 weeks for up to one year. After the final dose of MK-3475 each subject will be followed for 30 days for adverse event (AE) assessment. Serious adverse events (SAEs) and events of clinical interest (ECIs) will be collected for 90 days or until the initiation of new anti-cancer therapy, whichever comes first. Each subject will participate in the trial for up to approximately 18 months from the time the subject signs the Informed Consent Form (ICF) through the final Adverse Event Review.
Randomization Ratio	Initial randomization of 2:1 for neoadjuvant MK-3475 vs. untreated controls, with interim analysis influencing further randomization (see Sections 7.1.5.5 and 8.0).

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase I, randomized, no treatment controlled trial of neoadjuvant administration of MK-3475 (also known as pembrolizumab) in subjects with newly diagnosed RCC, ≥T1b (>4 cm diameter), to be conducted in conformance with Good Clinical Practices. Initially, subjects will be randomized 2:1 to receive either neoadjuvant MK-3475 or serve as untreated controls. Those to receive neoadjuvant MK-3475 will undergo image-guided core needle biopsy of their tumor with collection of a minimum of three cores of tumor tissue. Tissue from this block will be used by the local pathologist to confirm the diagnosis of RCC prior to the administration of MK-3475, and remaining tissue will be used for study analyses. Blood and urine samples for biomarker analysis will also be collected at the time of core biopsy in patients randomized to receive neoadjuvant MK-3475. Two to 3 weeks after the final neoadjuvant dose of MK-3475 (administered at a dose of 200 mg IV Q3 weeks), additional blood and urine will be collected for biomarker analysis and patients will undergo SOC RCC surgical tumor resection. Control patients will proceed to surgery, without receiving neoadjuvant MK-3475, with the collection of blood and urine samples for biomarker analysis on the day of surgery. In the operating room, three or more core needle biopsy specimens of the RCC may be collected before tumor removal and prior to renal artery cross-clamping under direct vision, at the discretion of the operating surgeon and subject to local institutional review board approval. Upon surgical removal of the tumor, a minimum of 10 cm^3 of non-necrotic resected tumor tissue will be collected and shipped as fresh tissue to Merck Research Laboratories for analyses. From the remaining resected tumor tissue, additional research samples will be collected for formalin fixation, snap freezing, and placement in RNAlater solution, while the remaining tumor tissue will be used by the local clinical site pathologist for routine clinical diagnostic purposes. Additional blood and urine samples for biomarker analyses will be collected from all subjects during post-operative follow up.

Following recovery from surgery, each subject may receive post-resection MK-3475. During this phase of the trial, subjects should be evaluated by SOC radiologic imaging at intervals to be selected by their treating physicians. The physician should utilize RECIST 1.1 and/or irRECIST for making clinical management decisions. AEs should be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Treatment with post-resection MK-3475 may continue until documented disease progression or recurrence, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, consent withdrawn by subject, start of new anti-cancer treatment, subject is lost to follow up, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 17 administrations of post-resection MK-3475 (approximately 1 year of treatment), or discontinuation for administrative reasons.

After the final study visit, routine SOC clinical follow up will continue. Since the majority of recurrences (83%) after surgical resection in RCC occur within 2 years of surgery [1], the clinical outcome will be queried for each subject 1 and 2 years following surgical tumor resection.

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.

This trial will use an adaptive design based on pre-specified criteria. There will be up to three formal interim analyses. The first interim analysis will be conducted after 9 subjects have entered the trial and the immune cell infiltrates in their surgically resected RCC specimens have been assessed. The second interim analysis will be conducted after 9 additional subjects have entered the trial and the immune cell infiltrates in their surgically resected RCC specimens have been assessed. The third interim analysis may be conducted when 9 additional subjects have entered the trial and the immune cell infiltrates in their surgically resected RCC specimens have been assessed. See section 8.0 – Statistical Analysis Plan, for additional details regarding sample size determination.

The interim analyses will include re-estimations of the sample size required to maintain power in the trial. If results of the interim analyses indicate that a larger sample size is necessary, subject enrollment may be extended. Details are described in Section 8.0 – Statistical Analysis Plan. If further extension of enrollment beyond the 36 subjects proposed in this protocol is needed, a protocol amendment will be filed.

Results of the first interim analysis will be used to determine if subsequent patients recruited to participate in the study will continue to be randomized to the untreated control group that does not receive neoadjuvant MK-3475 or whether subsequent patients enrolled in the study will all receive neoadjuvant MK-3475. This determination will be made according to the pre-specified algorithm described in detail in Section 8.0 - Statistical Analysis Plan.

Results from the first interim analysis will also be used to determine if the two dose regimen for neoadjuvant MK-3475 should be increased to 3 doses, according to the pre-specified algorithm described in detail in Section 8.0 – Statistical Analysis Plan.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

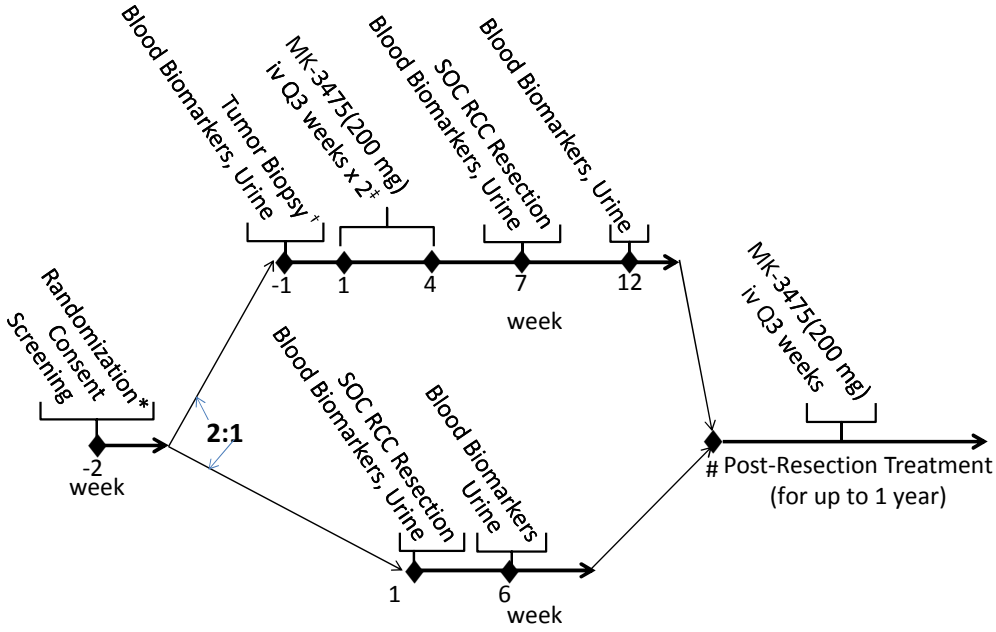


Figure 1 MK-3475-031 Trial Design

Patients with newly diagnosed RCC (≥T1b (>4 cm diameter)) will be screened for trial participation, and after informed consent is obtained will be assigned to either undergo percutaneous image-guided core needle tumor biopsy followed by neoadjuvant MK-3475 and then SOC surgical RCC resection (top arrow) or proceed directly to SOC surgical RCC resection (bottom arrow). After recovery from surgery, all subjects may receive post-resection MK-3475.

*Initially, patients will be randomized 2:1 to neoadjuvant MK-3475 vs. untreated control, but based on prespecified interim analysis endpoints, continued randomization to the control group may be discontinued.

†An additional study-prescribed pretreatment core needle biopsy is not required if a diagnostic biopsy has been performed per local SOC (and within 45 days prior to the first dose of MK-3475) and sufficient tissue is available from such a specimen for the study-related analyses specified for the pretreatment core biopsy.

‡If RCC immune cell infiltrates are not increased by at least two-fold in more than one of the initial 6 patients receiving 2 doses of neoadjuvant MK-3475, all subsequently enrolled subjects may receive 3 doses of neoadjuvant MK-3475.

#Upon recovery from surgery, all subjects may receive post-resection MK-3475, 200 mg IV, Q3W, for up to one year (17 doses).

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To assess the safety of neoadjuvant MK-3475 therapy in patients undergoing surgical resection for the treatment of RCC

Hypothesis: Neoadjuvant MK-3475 treatment will be well tolerated in patients undergoing subsequent surgical RCC tumor resection.

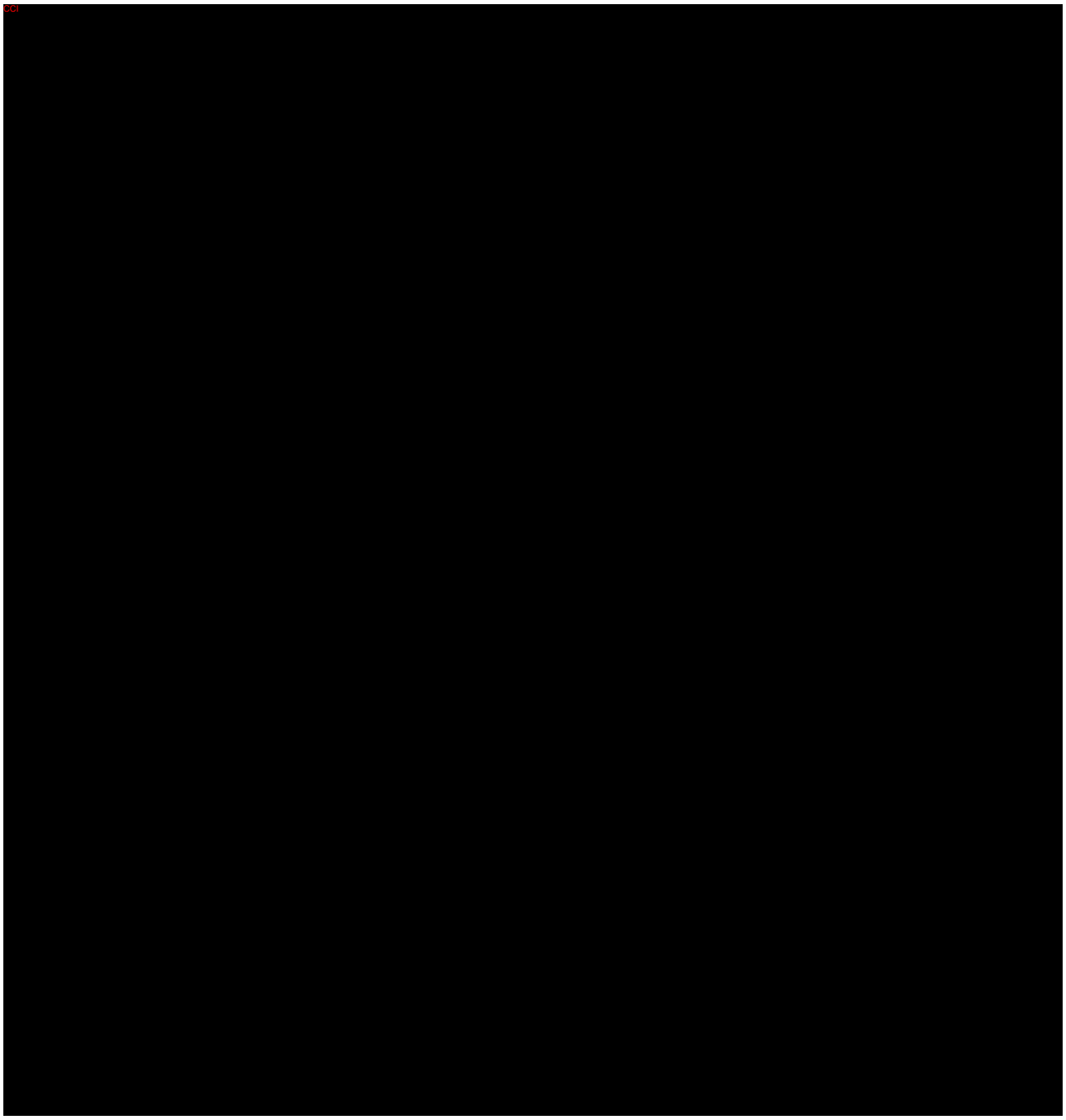
(2) **Objective:** To assess the effect of neoadjuvant MK-3475 therapy on immune cell infiltration in RCC

Hypothesis: Neoadjuvant MK-3475 therapy will stimulate a 2-fold or greater increase in intratumoral lymphocytic infiltration in at least 30% of patients with RCC.

3.2 Secondary Objective(s) & Hypothesis(es)

3.3 Tertiary Objectives

CCI



3.4 Exploratory Objectives

CCI

(8) **Objective:** To assess the effect of neoadjuvant MK-3475 therapy on IMR ligand expression by tumor cells in RCC

(9) **Objective:** To assess the ability of neoadjuvant MK-3475 to stimulate antigen-specific anti-tumor immune responses in patients with RCC

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

MK-3475 is a highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 thus exerts an immunomodulatory function by affecting the PD-1 pathway that regulates peripheral immune tolerance.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies [3-7]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant melanoma (MEL) and RCC. TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as MEL and RCC [8, 9].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement with its ligands (PD-L1 and/or PD-L2) [10,11]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [10; 12-14]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) as both molecules regulate an overlapping set of signaling proteins [15, 16]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and NK cells [17, 18].

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [15, 19-22]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [15]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 (and to a lesser extent of PD-L2) on tumor cells has been found to correlate with poor prognosis and survival in various cancer types, including RCC [23], pancreatic carcinoma [24], hepatocellular carcinoma [25], and ovarian carcinoma [26]. Furthermore, PD-1 also appears to regulate tumor-specific T-cell expansion in subjects with MEL [27]. This

suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

RCC is the seventh most common cancer among US men and ninth among US women. Twenty percent of people present with advanced disease, and an additional 30% of those who present with localized disease will eventually develop distant metastases and become largely incurable. Surgical resection of the primary tumor, even in the face of metastatic disease, remains SOC for treatment of RCC. In addition, systemic treatment using agents that target the vascular endothelial growth factor and its receptor as well as therapies against the mammalian target of rapamycin are standard options for metastatic disease. Cytokine-based treatment with interleukin-2 (IL-2) or interferon-α (IFN-α) were previously the mainstay of therapy for RCC and still benefit a small proportion of subjects. Despite seven new treatments being approved for treatment of metastatic RCC in last decade, there has been only a modest improvement in overall survival [28, 29]. Of particular relevance to this protocol, to date neoadjuvant therapy has not been shown to improve clinical outcome in RCC.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function *in vivo* [27, 30-34]. Experiments have confirmed the *in vivo* efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced MEL, non-small cell lung cancer, RCC, head and neck cancer, triple negative breast cancer, gastric cancer, bladder cancer and hematologic malignancies, as well as a variety of other cancer types. For trial details please refer to the IB**.**

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for the Trial

4.2.1.1.1 Rationale for Neoadjuvant MK-3475 in RCC

RCC is considered an immunogenic tumor, with reported episodes of spontaneous immune-mediated tumor regression, and as such is a logic candidate for immunotherapy. Immune modulation with high dose IL-2, a multitude of tumor vaccine approaches, as well as blockade of the CTLA-4 IMR using the mAb Ipilimumab have all shown clinical activity, further supporting the concept that RCC can respond to immune manipulation.

The expression of PD-L1, the primary ligand for PD-1, by RCC cells also supports the administration of MK-3475 in RCC to block this interaction and release intratumoral immune cells from PD-1 mediated suppression. In one study, increased expression of PD-L1 was found in 44% of primary RCCs and in 54% of metastatic RCC lesions. Importantly, RCC patients with high levels of tumor PD-L1 expression were more likely to die [35, 36]. Of note, RCC infiltration by NK cells, as detected using molecular profiling of NK cell associated genes, has also been shown to correlate with survival [37]. As PD-1 has been found to be expressed by NK cells, and blockade of PD-1 has been shown to augment NK activity [38], PD-1 blockade by MK-3475 could therefore potentially restore NK-mediated anti-tumor immunity in RCC patients.

The strongest rationale for administering MK-3475 in RCC is provided by the results of studies in which patients with RCC were treated with mAbs that block either PD-1 or its primary ligand PD-L1. In a phase I study in 32 patients with metastatic RCC treated with anti-PD-1 mAb (nivolumab) at IV doses of either 1 mg/kg or 10 mg/kg Q2weeks, the overall clinical response rate was 31%, with an overall duration of response of more than one year in 4/5 patients treated with the 10 mg/kg dose [39]. Grade 3-4 AEs were observed in 12% of subjects. Using an anti-PD-L1 mAb to block the interaction between PD-1 and its primary (but not only) ligand PD-L1, Cho treated patients with metastatic RCC, observing progression free survival of 50% at 24 weeks, with Grade 3-4 AEs attributable to the study drug occurring in 13% of patients [40].

While the use of neoadjuvant PD-1 blockade in RCC has not yet been reported, neoadjuvant therapy of RCC using targeted antiangiogenic drugs has been reported. Such therapy has not been associated with an increase in overall complications from surgical RCC resection, but was noted to be an independent risk factor for the development of postoperative wound infection [41]. As anti-PD-1 mAb functions to enhance immune responses and does not appear to have an inhibitory effect on angiogenesis (a process critical for wound healing), such an increase in wound complications would not be expected with neoadjuvant administration of MK-3475.

4.2.1.1.2 Rationale for Post-Resection MK-3475 in RCC

4.2.1.1.2.1 Rationale for Adjuvant MK-3475 in Subjects with Fully Resected RCC

Patients with RCC and no evidence of metastatic disease at diagnosis have a risk of relapse as high as 35% or 40% [42-44].

For patients with a partial or radical nephrectomy, the risk or recurrence largely depends on tumor size, grade, stage, histology, performance status, and completeness of resection [45-47]. Currently, pathologic tumor stage is the single most important prognostic factor in resected RCC but does not fully explain disparities in survival among stages [48]. Some other histologic features, such as Fuhrman grade, histologic subtype, and presence of necrosis or sarcomatoid component have been linked with a poorer prognosis [49]. Regarding histologic subtypes, chromophobe and papillary type I seem to have a more indolent clinical course, and papillary type II and clear-cell RCC show a more aggressive behavior [47].

A systematic review with meta-analysis of adjuvant therapies for locally advanced renal cell cancer was published in 2011 [50]; it concluded that there was no support for using systemic therapy in the adjuvant setting, as there was no evidence of any benefit and there was evidence of substantial toxicity. The therapeutic modalities included in that study were mainly chemotherapy, immune therapies, and hormonal treatments, since no trial with targeted therapies had been completed at that time.

Immunotherapy was one of the standard options for metastatic RCC before the advent of targeted therapies. Interleukin-2 and interferon (IFN) were commonly used in that setting but with poor results, achieving a response rate of 6% to 10% with some durable responses, and a median OS of 12 to 15 months [51]. Nevertheless, none of the adjuvant trials with such immune therapies has been successful. Two trials compared IFN with placebo in T3 to T4 and/or node-positive patients, without improvements in DFS or OS [52, 53]. Two other small trials that explored the role of IL-2, whether in monotherapy as a single-dose treatment [54] or combined with IFN [55], also had negative results. A triple combination of IL-2, IFN, and 5-fluorouracil also failed to show an improvement in DFS compared with placebo and was associated with significant toxicity [56]. This same schedule was tested in a different trial, showing no differences in DFS but a worse OS for the treatment arm [57]. Some other trials have explored the potential role in the adjuvant setting of therapeutic vaccines.

Therefore, until October of 2016, no treatment had demonstrated substantial and consistent benefit in the adjuvant setting for RCC, whether using immunotherapy, radiotherapy, hormonal therapy, or chemotherapy. Trials testing targeted therapies such as sunitinib, sorafenib, pazopanib, and axitinib have either failed or are ongoing, but appear to cause significant toxicities in patients with no existing disease burden during treatment [42, 43].

In October 2016, results from a Phase III randomized, placebo-controlled study in patients with high-risk clear-cell RCC who had undergone nephrectomy (S-TRAC) showed a median duration of DFS that was significantly longer in the sunitinib group (6.8 years; 95%

confidence interval [CI]: 5.8 to NR) compared with the placebo group (5.6 years; 95% CI: 3.8 to 6.6), with a hazard ratio (HR) of 0.76 for blinded independent radiologic review. Overall survival data were not available at the reported data cutoff. Dose reductions due to AEs were more frequent in the sunitinib group than in the placebo group (34.3% vs. 2%), as were dose interruptions (46.4% vs. 13.2%) and discontinuations (28.1% vs. 5.6%). Grade 3 and 4 AEs were more frequent in the sunitinib group (48.4% and 12.1%, respectively) than in the placebo group (15.8% and 3.6%, respectively). The incidence of SAEs in the groups was similar (21.9% for sunitinib vs. 17.1% for placebo); no deaths were attributed to toxic effects related to study treatment [58].

These recent data are encouraging, as technically this is the first study to show a positive DFS in this patient population; however, the treatment discontinuation rate remained high and the main AEs were the primary driver for limited treatment duration.

Given recent preliminary signs of both clinical activity and tolerability of checkpoint inhibitors in clinical trials in the adjuvant setting of RCC treatment, pembrolizumab may be expected to demonstrate a similar efficacy and safety profile in this setting.

4.2.1.1.2.2 Rationale for Post-Resection MK-3475 in Patients with Metastatic Disease at the Time of RCC Resection

The anti-PD-1 mAb nivolumab has subsequently received FDA approval for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy, based on a Phase III randomized, open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. In that study, patients were randomized to nivolumab (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with everolimus (median survival of 25 months vs 19.6 months, respectively (p=0.0018). Of note, nivolumab as well as pembrolizumab (MK-3475) are both currently being evaluated in clinical trials in the first-line setting for the treatment of metastatic RCC.

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 improvements 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 vs pazopanib trial [59]. In a meta-analysis by Heng et al. on 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 [60]. Based on Surveillance, Epidemiology, and End Results (SEER) data from 2004-2010, the 5-year survival rate of advanced RCC was only 12% [61]. Therefore, further development of novel agents, such as MK-3475, with durable clinical benefit and curative effect is still highly needed for advanced RCC. This low survival rate and lack of a durable response in patients with advanced RCC treated with the

available SOC agents (i.e. antiangiogenic agents) provides a strong rationale for moving to MK-3475 treatment in the post-resection Phase of this study without requiring patient with metastatic RCC at the time of RCC resection to fail post-resection anti-angiogenic therapy before initiating MK-3475 treatment.

4.2.1.2 Rationale for Selected Study Population

Patients with RCC have been selected for this study for a variety of reasons. First, renal tumors are amenable to percutaneous core needle biopsy, allowing collection of tumor tissue for confirmation of the diagnosis of RCC prior to MK-3475 administration and for critical baseline analyses, with minimal potential morbidity. Secondly, there is no standard of care neoadjuvant therapy for RCC, and as such, the administration of MK-3475 in a neoadjuvant setting will not displace a SOC therapy. Third, RCC has been shown to be immunogenic and some cases of RCC have responded to immunotherapy. As such, the immune-stimulatory effects of PD-1 blockade using MK-3475 might be expected to enhance anti-RCC immune responses.

Patients with metastatic RCC are specifically not excluded from participating in this study, because surgical resection of the primary tumor is the first line of treatment, even in those patients with metastatic disease, provided the primary tumor is amenable to resection. In a prospective randomized study, Flanigan, et al, found that in patients with metastatic RCC, nephrectomy followed by systemic interferon α-2b therapy significantly prolonged survival when compared to interferon therapy alone [62]. In a similar trial in metastatic RCC, Mickinsch, et al, also found that surgical resection of the primary tumor provided a statistically significant survival benefit over therapy with interferon α-2b alone [63]. For patients with metastatic RCC, cytoreductive nephrectomy prior to any systemic therapy is supported by results from two prospective randomized phase 3 trials comparing nephrectomy followed by IFN-α therapy vs IFN-α therapy alone. In both those studies, significantly improved overall survival was observed in patients receiving cytoreductive nephrectomy followed by IFN-α [41]. Until ongoing trials evaluating the utility of cytoreductive nephrectomy prior to anti-angiogenic therapy are completed, the current standard of care for patients with metastatic RCC who are operative candidates remains surgical removal of the primary tumor [41].

4.2.1.3 Rationale for Sample Collection in This Trial

Discovery Sciences at Merck has a critical unmet need for clinical specimens from patients being treated with MK-3475 to help elucidate the mechanism of action of PD-1 blockade and to both identify new targets for immune modulation and guide the selection of IMRs for blockade in combination with MK-3475. This study is designed specifically to collect these critical specimens in RCC patients receiving MK-3475 in a neoadjuvant setting. Upon completion of this study, we will more fully understand the mechanism of action by which MK-3475 stimulates anti-tumor immunity, we will more clearly understand the changes in IMR expression profiles of immune cells within RCC tumors that occur during MK-3475 treatment, we will have identified numerous biomarkers potentially predictive of immune

responses stimulated by MK-3475, and we will have identified new IMR targets for Discovery Sciences to further interrogate.

4.2.1.4 Rationale for Intraoperative Core Needle Biopsies in This Trial

As presented at the 2014 American Society of Clinical Oncology (ASCO) meeting, Geyde, et al, noted that in RCC, gene expression profiles in biopsy tissue are significantly altered by warm ischemia [64]. Specifically, they found that gene expression profile of RCC tissue obtained by intraoperative core needle biopsy immediate prior to renal artery cross-clamping differed markedly from that obtained from analysis of RCC tissue collected after the tumor was resected, due to warm ischemia of the non-perfused tumor after renal artery cross-clamping. Based on this data, it is imperative that to most accurately compare gene expression profiles between RCC tissue collected pre-treatment by percutaneous core needle biopsy (of the normally perfused tumor *in vivo*) and RCC tissue collected at the time of surgery, such post-treatment RCC tissue should ideally be collected intraoperatively prior to renal artery cross-clamping in order to avoid RCC tissue ischemia-related gene expression changes that would be unrelated to MK-3475 treatment.

Based on anecdotal reports, some urologists may be concerned that such intraoperative core needle biopsies could "violate" the renal capsule and spill tumor cells, leading to delayed local tumor recurrences. However, the risk of this occurring is minimal, based on two perspectives; from the perspective of needle tract seedling during radiologically guided biopsies and from the perspective of intraabdominal seeding during surgery.

Percutaneous biopsy seeding is so rare that as of 2012 approximately 5 such problematic cases had been described [65, 66]. Port site seeding after laparoscopic RCC resection is also rare, even when the tumor is morcellated prior to removal, further supporting the concept that RCC does not readily metastasize in this fashion [67, 68]. Importantly, RCC enucleation has been promoted as a safe alternative to resection with margins, suggesting that the invasive edge of RCC is not at the physical boundary of the tumour [69]. Finally, even large RCC tumors that extend through the capsule of the kidney clinically do not lead to omental metastatic disease or cause ascites, again suggesting that RCC does not readily spread to the peritoneal cavity by tumor cell leakage.

For these reasons, we conclude that intraoperative core needle RCC biopsies obtained immediately prior to renal artery crossclamping are not only safe, but are also critical for obtaining accurate intratumoral gene expression profiling information for this study. Such accurate information will help to better inform on MK-3475 mechanism of action, better identify biomarkers of response to MK-3475 treatment, and better identify new targets for cancer immunotherapy, all of which will contribute to improved treatments for patients with RCC as well as other malignancies. It is understood that intra-operative core needle biopsy will be performed at the discretion of the operating surgeon and subject to local IRB approval.

4.2.1.5 Rationale for Key Hypothesis

Primary hypothesis (1) *Neoadjuvant MK-3475 treatment will be well tolerated in patients undergoing subsequent surgical RCC tumor resection*. MK-3475 therapy has been safe and effective in patients with a variety of different cancer types in the metastatic disease setting, including in patients with RCC, and none of the adverse effect observed to date should significantly impact patients undergoing surgical tumor resection.

The administration of only a limited course (two or three doses) of MK-3475 in the neoadjuvant setting as proposed in this protocol may lead to a lower incidence of treatment-associated SAEs than has been observed when patients with metastatic disease received extended (up to two years of) treatment with MK-3475. As shown in Figure 2, for patients with metastatic melanoma receiving MK-3475 every two or three weeks until disease progression, the overall incidence of AEs increased over the cumulative time of therapy, with approximately 47% of subjects experiencing serious (Grade 3-5) AEs after 300+ days of MK-3475 treatment. As can also be seen in Figure 2, at the times corresponding to the length of exposure that subjects in this trial will experience after 2 or 3 doses of neoadjuvant MK-3475 administered Q3W, the incidences of Grade 3-5 AEs were approximately 11% and 18%, respectively. Thus, during the administration of this limited course of neoadjuvant MK-3475 in this trial, the incidence of SAEs is expected to be markedly lower than has been reported to date with MK-3475 treatment.

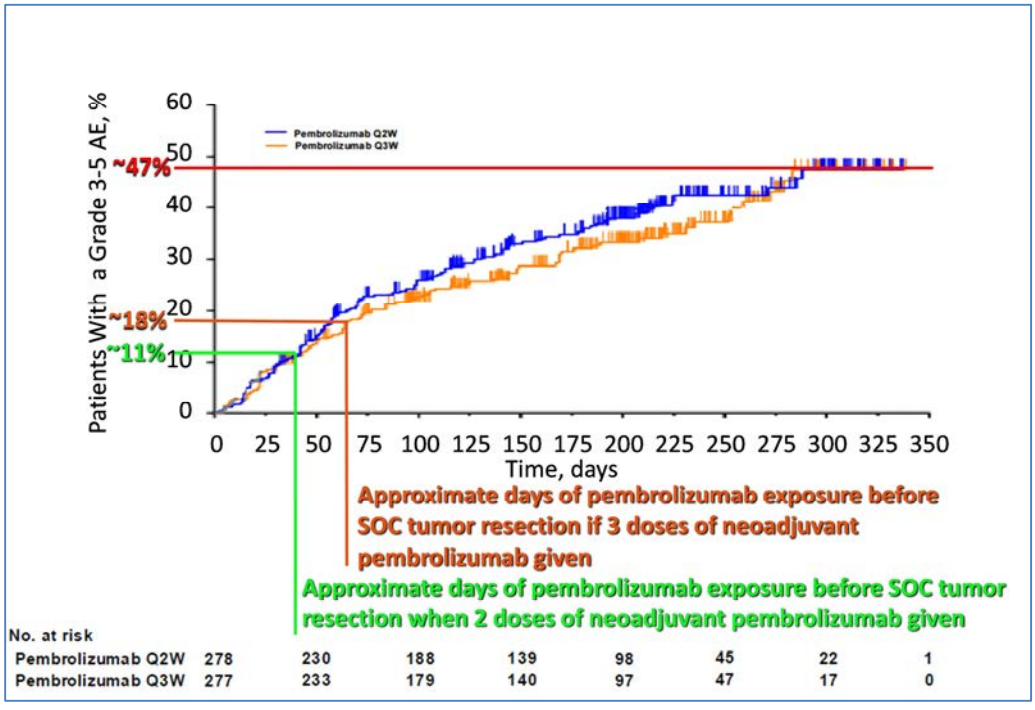
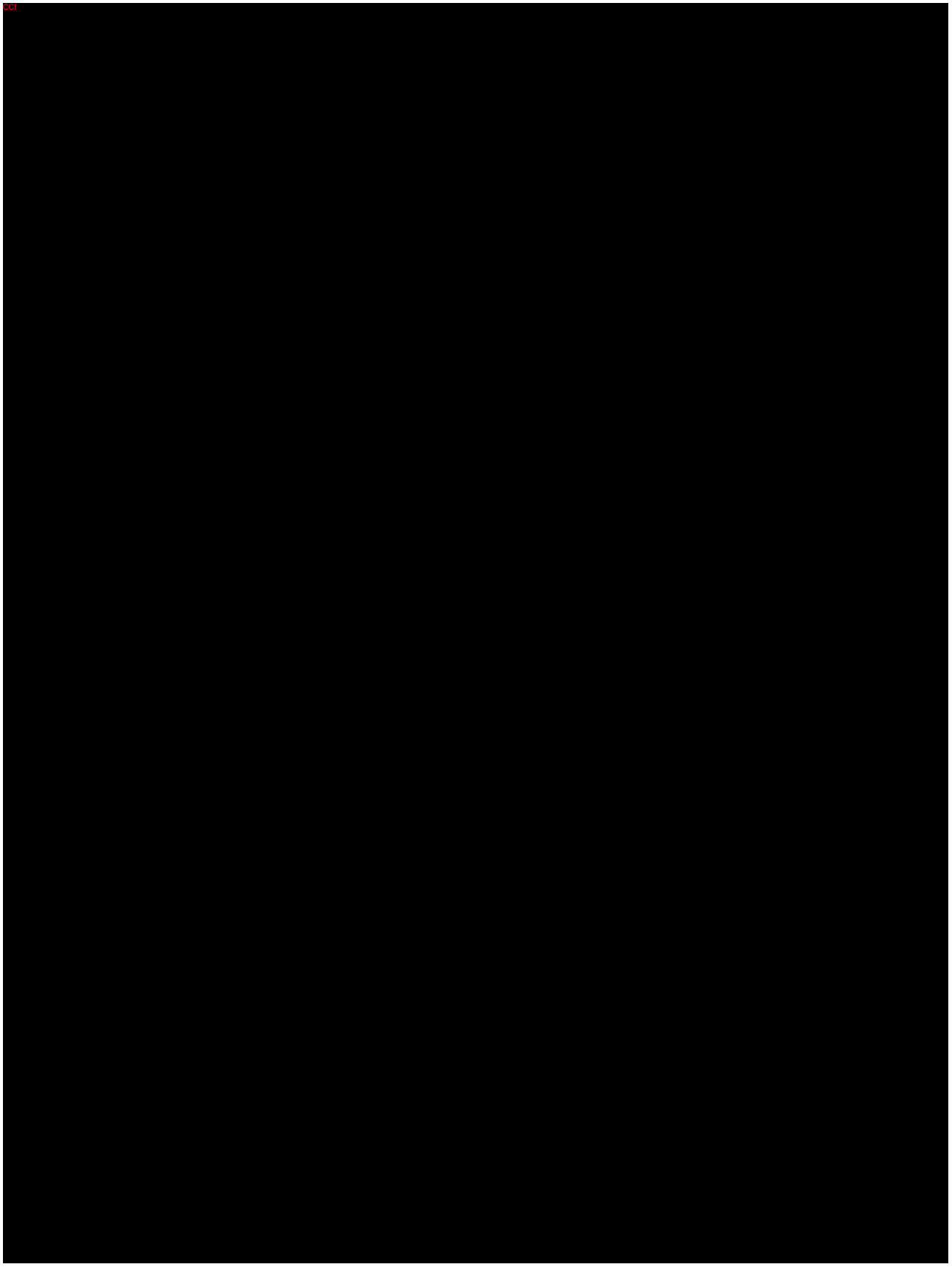


Figure 2 Relationship Between AEs and Time on Pembrolizumab (MK-3475) Therapy

Kaplan-Meier estimates of time to first adverse event of Grade 3, 4, or 5 severity, regardless of attribution to study treatment, in the all-patients-as-treated population in a clinical study in patients with metastatic melanoma (adapted from Figure S2 [70]).

Once this proposed study demonstrates the safety of neoadjuvant MK-3475, larger clinical studies assessing changes in survival and recurrence rates after neoadjuvant PD-1 blockade with MK-3475 in patients with RCC, as well as other malignancies, can be performed.

Primary hypothesis (2) *Neoadjuvant MK-3475 therapy will stimulate a 2-fold or greater increase in intratumoral lymphocytic infiltration in at least 30% of patients with RCC.* Based on preclinical studies using PD-1 blockade in *in vitro* models, studies using PD-1 blockade in *in vivo* tumor models, and clinical studies using MK-3475 in a variety of human malignancies, blockade of PD-1 is expected to enhance anti-tumor immunity and stimulate immune cell infiltration into RCC tumor tissue. Prior human studies have demonstrated that approximately 30% patients with metastatic RCC will clinically respond to therapy with mAbs that block PD-1. In addition, in a clinical study in MEL, MK-3475 treatment stimulated a more than 2-fold increase in CD8+ T cell infiltrates within metastatic tumors in a majority of patients with clinical responses [71]. In contrast, in none of the MEL patients with progressive disease during MK-3475 treatment did CD8+ T cell infiltrates increase. This suggests that an increase of at least 2-fold in RCC immune cell infiltrates will be observed in approximately 30% of RCC patients receiving MK-3475 in this study.



4.2.2 Rationale for Dose Selection/Regimen/Modification

Modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 7.1.5.8 - Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters.

The safety and efficacy of multiple different dose/schedules combinations have been explored in multiple clinical trials. Extensive data support a fixed MK-3475 dose of 200 mg IV Q3 weeks. The discussion below provides justification for this dosing in this protocol.

In the first in human study (Protocol number 001, refer to IB), which treated a variety of tumor types, MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). The dose level of 10 mg/kg Q3W was evaluated in previously treated subjects with NSCLC in Part C of Protocol 001.

PK data analysis of MK-3475 administered Q2W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). PD data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and PD data provided scientific rationale for testing Q2W vs. Q3W dosing schedules. Previously

treated subjects with NSCLC in PN001 Part C have experienced durable objective responses with acceptable toxicity when treated with MK-3475 at 10 mg/kg Q3W.

Data both from subjects with MEL and with NSCLC demonstrates objective responses to MK-3475 administered at the 2 mg/kg Q3W dose and schedule. In addition, given the lack of a dose response to date, modeling and simulation data indicate that a fixed dose of 200 mg provides adequate exposure for the largest sized subjects while not exceeding the exposure seen at 10 mg every 3 weeks in the smallest sized subjects. A population PK analysis has been performed using serum concentration time data from 476 subjects. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Simulations were performed on the basis of the population PK model, using a distribution of body weight reflective of the general population obtained from the National Health and Nutrition Examination Survey (NHANES) 2009-2010 database. Differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the MEL indication. The population PK evaluation also revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and MEL indications. Therefore, there are no anticipated changes in exposure between different indication settings, including RCC. Thus, a fixed dose of 200 mg Q3W will result in adequate exposure to MK-3475 across all body weights, similar to the exposures obtained with a 2 mg/kg Q3W regimen.

4.2.2.1 Rationale for the Use of Comparator/Placebo

Because the use of a placebo would entail an added delay of more than 5 weeks between diagnosis of RCC and SOC surgical tumor resection, with no potential for any clinical benefit, this study will not utilize a placebo control.

4.2.2.2 Starting Dose for This Trial

The starting dose of MK-3475, 200 mg IV, is based on extensive clinical data (see above). The 200 mg fixed dose is identical to that selected for FDA filings for MK-3475 approval in a variety of cancers.

4.2.2.3 Maximum Dose/Exposure for This Trial

The dosage of MK-3475 for this trial is fixed at 200 mg IV Q3W. Initial plans are to administer a total of two neoadjuvant doses to each subject, but this may be increased to three total doses, based on the first interim analysis (See Section 8.0- Statistical Analysis Plan) as stipulated in Section 7.1.5.8- Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters. Therefore the maximum exposure prior to surgical RCC resection in those subjects randomized to neoadjuvant MK-3475 will be 600 mg per subject. Following RCC resection and recovery from surgery, all subjects may receive MK-

3475, 200 mg IV, Q3W, for up to 1 year (17 doses), for a maximal exposure in the post-operative period of 3.4 gm. The maximal total exposure on trial will therefore be 4 gm per subject.

4.2.2.4 Rationale for Dose Interval and Trial Design

The dosing interval (Q3W) and number of doses (2) for MK-3475 (200 mg dose) in the neoadjuvant portion of this study is based on several considerations. The Q3W interval is based on the results of clinical MK-3475 studies comparing Q2W with Q3W dosing intervals in which no difference in clinical efficacy was observed. Secondly, the decision to administer two (possibly three) neoadjuvant doses of MK-3475 is based on clinical considerations.

MK-3475 will be administered during a 5-6 week interval prior to surgery, which is considered clinically acceptable in the RCC neoadjuvant context for a drug with a proven mechanism of action. While this 5-6 week delay may cause potential anxiety for the patient and/or the physicians treating the patient, this relatively short delay should have no clinical impact. Based on a 2006 report, the average size of renal cell cancers is approximately 6 cm in diameter [72]. With the growth rate of RCCs of between 0.1 to 1.35 cm/year [73], the average lesion has been present for over 4 years if one assumes the highest rate of growth in this range. A 6 week interval in such an instance corresponds to at most a 2.5% increase in the time from initial renal cell malignant transformation to surgical resection. As such, a 6 week interval between diagnosis and surgical resection is clinically insignificant. In addition, all patients in this trial who will be experiencing this interval between diagnosis and SOC surgical RCC resection will be receiving MK-3475 during this period, with the potential for clinical benefit. Of note, this study does not include placebo administration in the control patients in order to avoid any delay between diagnosis and SOC surgical RCC resection in subjects not receiving neoadjuvant MK-3475.

It is also highly likely that a period of time of at least 5-6 weeks will be necessary for MK-3475 to stimulate an anti-tumor response that manifests as an immune cell infiltration of the primary tumor. In a study in patients with metastatic melanoma, significant increases in CD8+ T cell infiltrates were observed in tumor biopsies collected after 3-8 weeks of MK-3475 therapy in the majority of patients who responded clinically to therapy [71]. Importantly, in four of five patients with delayed clinical responses to therapy, increases in tumor TIL's were not observed in tumor biopsies collected 3-8 weeks following initiation of MK-3475 therapy but were later observed in biopsies collected 80-120+ days following treatment initiation. The variability of the time interval between the initiation of MK-3475 therapy and tumor biopsy in that melanoma study precludes a precise estimation of length of time needed for MK-3475 to augment anti-tumor responses and stimulate infiltration of the tumor with immune cells. We anticipate that immunologically, the tumor, present during this period of neoadjuvant therapy with MK-3475, will serve as an important source of both RCC antigen-specific T cells and tumor antigens for stimulating anti-tumor immune responses in this setting, and that without the presence of the tumor, MK-3475 might not be able to stimulate an effective anti-tumor immune response. As discussed in Section 8.2.6 (Interim Analysis), if at least a 2-fold increase in immune cell infiltrates is not seen in more than one

of the first 6 subjects that receive 2 Q3W doses of MK-3475, we may increase to three the number of Q3W doses that subsequent subjects receive, primarily to allow more time for the tumor to be exposed to MK-3475 and therefore facilitate the stimulation of anti-tumor immunity and immune cell infiltration of the primary tumor.

This increase in the number of doses would lengthen the delay time to surgery from 5-6 weeks (2 doses) to 8-9 weeks (3 doses). This slightly increased delay remains clinically insignificant for the same reasons that a 5-6 week delay is clinically insignificant, as described above. Specifically, for an 8-9 week delay, with the growth rate of RCCs of between 0.1 to 1.35 cm/year [73], the average RCC lesion has been present for over 4 years if one assumes the highest rate of growth in this range. A 9 week interval in such an instance corresponds to at most a 4.3% increase in the time from initial renal cell malignant transformation to surgical resection. As such, a 9 week interval between diagnosis and surgical resection remains clinically insignificant. In addition, all patients in this trial who will be experiencing this interval between diagnosis and SOC surgical RCC resection will be receiving MK-3475 during this period, with the potential for clinical benefit.

In this protocol, all subjects may receive up to 1 year of post-resection MK-3475 at a dose of 200 mg Q3W once they have recovered from surgery. As discussed previously (Section 4.2.2), this dosing regimen is supported by extensive clinical data.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of MK-3475 administered in a neoadjuvant setting in patients with RCC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades, including serious adverse events (SAEs) and events of clinical interest (ECIs), experienced by all subjects who have received MK-3475.

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs to be analyzed will include but will not be limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, potential immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

Because all patients with RCC treated with neoadjuvant MK-3475 in this trial will undergo subsequent SOC operative tumor resection, surgical complications will be assessed. The following information related to surgery will be recorded: blood transfusions in the perioperative period, length of hospital stay, readmission, and surgical complications including the need for surgical re-exploration, thromboembolic events, cardiovascular events, pulmonary complications, gastrointestinal complications, postoperative infection, and incision-related complications.

4.2.3.2 Efficacy Endpoints

Immune cell infiltration of RCC. The primary efficacy objective of this trial is to determine the effect of neoadjuvant MK-3475 on intratumoral immune cell infiltration in patients with RCC. In order to assess changes in tumor immune cell infiltrates, each subject randomized to receive neoadjuvant MK-3475 must either undergo a study-prescribed pretreatment image-guided percutaneous RCC biopsy or have already undergone a diagnostic core-needle biopsy performed as per local SOC (and within 45 days prior to the first dose of MK-3475) from which sufficient tissue is available and will be provided for the study-related analyses specified for the pretreatment core biopsy. Tissue from either such biopsy will be used to confirm the diagnosis of RCC prior to the administration of MK-3475 and for assessment of baseline immune cell infiltration of each subject's RCC prior to MK-3475 treatment. At the time of SOC surgical tumor resection, RCC tissue will also be collected for analysis of immune cell infiltrates, both from control patients and those receiving a full course of neoadjuvant MK-3475.

Immune cell infiltration into RCC tissue will be assessed using three methods. First, IHC of sections of FFPE tissues will be utilized to enumerate specific lymphocyte populations infiltrating the tumor, with markers to include CD3, CD8, and FoxP3. Secondly, DNA will be extracted from the FFPE core biopsy tissue as well as from FFPE and frozen resected tumor specimens and promoter methylation analysis will be performed to quantitate T cell infiltrates [74]. Third, the same DNA will be subjected to TCR sequencing analysis for quantitating T cell infiltration and for determining clonality of the tumor infiltrating T cells.

Alterations in TIL IMR expression. This trial is also designed to assess changes in IMR expression by TILs in response to therapy with MK-3475. Fresh RCC tumor tissue will be collected from each patient (controls and those receiving neoadjuvant MK-3475) at the time of SOC RCC surgical resection. In the operating room immediately after the tumor specimen is removed from the patient, a minimum of 10 cm^3 of resected RCC tumor tissue will be collected as fresh tissue, placed in transport medium, and shipped overnight to the Merck laboratories. Once received in the laboratory, fresh tumor tissue will be enzymatically digested and the phenotype and IMR expression profiles of the TILs will be assessed using a panel of mAbs and flow cytometry.

Clinical Efficacy. This trial is not designed to assess clinical efficacy, and this study is not powered to detect an effect of neoadjuvant and/or post-resection MK-3475 treatment on clinical outcome measures. Because all subjects may receive additional MK-3475 after they have recovered from surgery, the impact of neoadjuvant therapy on response also cannot be assessed in this trial.

The pre-operative imaging studies on which the diagnosis of RCC was based for each study participant as well as postoperative scans for those subjects with metastatic disease at the time of enrollment may be requested and held for possible further analysis. Supportive retrospective central review of imaging studies may be performed for this study using RECIST 1.1 and volumetric analysis.

RCC recurrence and patient survival will be queried at 1 and 2 years after surgical RCC resection. Patient survival and RECIST-based responses will be queried, but again, this study is not powered to detect an effect either neoadjuvant or post-resection treatment with MK-3475 treatment on any clinical outcome measure.

4.2.3.3 Planned Exploratory Biomarker Research

Biomarker research to identify factors important for MK-3475 treatment responses will be pursued. Tissues to be collected and assays to be performed include but are not limited to the following:

Gene expression profiling

RNA extracted from FFPE core biopsy tissue, FFPE resected RCC specimens, fresh resected RCC tissue in RNAlater solution, and whole blood will be utilized for gene profiling. Pretreatment gene expression profiles may predict which RCC tumors are infiltrated by immune cells in response to MK-3475 therapy. By comparing profiles in tumor tissues and whole blood collected before and after neoadjuvant MK-3475, changes in gene expression induced during MK-3475 treatment will be identified and will be used to more fully understand the mechanism of action of MK-3475.

Blood collection for genomic, genetic, and proteomic analysis

Blood will be collected at the time of biopsy (baseline), at the time of surgical tumor resection, and one month postoperatively. Blood collected in Paxgene tubes will also be used for DNA extraction and subsequent sequencing-based TCR utilization analysis (for correlation with intratumoral TCR utilization). Additional blood collected in Paxgene tubes will be used for RNA extraction and subsequent gene profiling for comparison to and correlation with tumor gene profiles. Whole blood samples will be analyzed by flow

cytometry to determine the phenotype of PBMC, and for subject that are HLA-A2+, pentamer staining will be performed (see below). PBMC will also be isolated from whole blood and then cryopreserved for later functional analysis.

Plasma and serum will also be collected and frozen for later analysis. Assays to be performed using plasma or serum may include but will not be limited to measurement of sPD-L1 levels using an ELISA assay recently developed at Merck, protein profiling, miRNA profiling, exosome isolation and analysis, assessment of serum antibodies, and circulating tumor DNA analysis. A recent study suggested that miRNAs 21 and 378 levels in plasma were predictive of response in patients with metastatic RCC treated with everolimus [78].

Determining the influence of tumor tissue source (FFPE vs frozen tissues) on DNA-based methods for quantitating RCC T cell infiltration

In addition to fresh tumor tissue, additional RCC tumor tissue samples will be collected at the time of nephrectomy. Tumor tissue will be fixed in formalin and then paraffin embedded, while additional pieces of tumor tissue will be snap frozen and used for DNA extraction and additional pieces will be placed in RNAlater solution for RNA extraction. As described above for the analysis of the core biopsy tissue, infiltration by T cells will be assessed using three approaches. In addition, DNA extracted from frozen tumor tissue may be analyzed using the two DNA-based T cell infiltration assessment approaches described above. This will allow a comparison of molecular T cell analysis using formalin fixed vs fresh frozen tissue and inform on the need for collection of frozen tumor tissue in subsequent studies using these DNA-based approaches. As formalin fixation and paraffin embedding has a variable effect on the integrity of DNA extracted from such tissues, comparing results derived from the analysis of DNA extracted from FFPE vs frozen tissues should also allow us to assess the accuracy of performing these types of assays using DNA extracted from archived FFPE tissues.

PBMC Phenotypic Assessment

Whole blood will be collected at the time of pretreatment core needle biopsy (for those patients randomized to receive neoadjuvant MK-3475), perioperatively, and in follow up for assessment of phenotype using flow cytometry. Expression of lineage markers, activation markers, and IMRs will be assessed. In addition, when a given patient is HLA-A2+, tetramer staining will be performed to characterize the phenotype of RCC antigen-specific T cells in the blood.

Measurement of Tumor miRNA levels

miRNA profiling may be performed using RNA extracted from RCC tumor tissue.

Urine Exosome Analysis

Urine will be collected at the time of pretreatment core needle biopsy (for those patients randomized to receive neoadjuvant MK-3475), perioperatively, and in follow up, and will be frozen. Exosome analysis may subsequently be performed.

Tumor histoculture

A portion of fresh resected RCC tissue may be used for histoculture. Briefly, this unique approach developed by our discovery scientists entails incubating thin tumor tissue slices in medium, modulating IMRs with mAbs added to the medium, and measuring the secretion of cytokines by T cells residing within the tumor.

Assessment of IMR Expression by RCC tumor cells

Digested tumor cells may be analyzed for expression of PD-L1 and PD-L2 using specific fluorochrome-labeled Abs and flow cytometry. Expression of other IMR ligands may also be assessed. Digested tumor tissue cells in suspension may also be cryopreserved after TIL and tumor cell analysis. These RCC cells may later be used as targets for immune-based assays to measure tumor-specific responses in cryopreserved PBMCs.

Isolation and cloning of intratumoral B cells secreting anti-RCC Abs

B cells isolated from peripheral blood may be transformed and cloned and the Abs secreted will be screened for reactivity against RCC cells.

Induction of RCC antigen-specific T cells in peripheral blood in response to MK-3475 treatment

PBMC isolated from peripheral blood may be assessed for antigen specificity using an IFN-γ ELISpot assay and stimulation with overlapping pools of peptides from known RCC antigenic proteins. Other approaches for measuring immune reactivity of these PBMCs may also be utilized.

4.3 Exploratory Biomarker Objectives

(1) Objective: To evaluate the differences in the IMR expression profiles between RCC tumor antigen-specific CD8+ T cells and unselected TILs in patients that are HLA-A2+ using tetramers

Purpose: When compared to bulk TILs, tumor antigen-specific T cells may express different IMRs [76, 77]. As tumor antigen-specific T cells are the critical mediators of T cell-mediated destruction of tumor cells, knowledge of the specific IMRs expressed by these T cells in response to MK-3475 will be critical for rational selection of additional IMR targets for therapy in combination with MK-3475.

(2) **Objective:** To use clinical response data from the study patients with metastatic disease that receive neoadjuvant MK-3475 to potentially identify the correlation between clinical response and tumor immune cell infiltration

Purpose: The primary hypothesis that MK-3475 will stimulate a 2-fold or greater increase in tumor immune cell infiltrates in 30% of RCC patients treated with neoadjuvant MK-3475 is based on clinical study results, but whether the increase in immune cell infiltrates occurs in the 30% of patient with RCC who respond to PD-1 blockade is unknown. Clinical responses in the subset of patients with metastatic disease that receive neoadjuvant MK-3475 may allow tumor responses and immune responses to be correlated.

(3) **Objective:** To evaluate baseline as well as changes in levels of serum/plasma biomarkers, including but not limited to sPD-L1, miRNAs, proteins, antibodies, nucleic acids and exosomes after neoadjuvant MK-3475 therapy as potential biomarkers of the immune response to treatment

Purpose: Blood-based biomarkers predictive of response to MK-3475 would be valuable for future patient selection, while those that provide an early readout of response would be valuable for modifying patient therapy. This study will seek to identify potential blood-based biomarkers appropriate for subsequent validation in larger studies.

(4) **Objective:** To evaluate differences in tumor tissue miRNA expression levels in response to treatment with MK-3475

Purpose: Changes in tumor miRNA expression profiles may help identify mechanisms of resistance to MK-3475 therapy.

(5) **Objective:** To isolate and transform B cells that secrete mAbs that specifically recognize RCC tumor antigens from the peripheral blood of RCC patients treated with MK-3475

Purpose: Relatively little is known about the role of B cells and antibody responses in tumor immunity. It is possible and likely that PD-1 blockade with MK-3475 will act to reverse anergy not only in tumor-specific CTL but also in tumor antigen-specific helper T cells that provide help to B cells producing tumor antigen-specific antibodies. It is thus possible that in MK3475 treated patients both cellular and humoral responses contribute to efficacy and tumor-specific antibodies with therapeutic potential are present and can be characterized.

(6) **Objective:** To evaluate urine exosomes as a potential biomarker of immunologic response to neoadjuvant MK-3475 treatment

Purpose: Exosomes in urine may offer a readily available source of biomarkers to predict response to MK-3475 in RCC.

(7)

(8)

(9)

4.3.1 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens routinely and specifically collected 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. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis

and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.4 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

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 newly diagnosed 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/assent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be ≥18 years of age on day of signing informed consent.

3. Have newly diagnosed RCC, with a primary tumor diameter of more than 4 cm (≥ T1b), not previously treated, and be a candidate for operative tumor resection.

4. Be willing and able to undergo pre-treatment baseline image-guided core biopsy of their primary RCC (unless a diagnostic biopsy has already been performed within 45 days prior to the first dose of MK-3475 and sufficient RCC tissue is available for study-related analyses).

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1, based on screening labs.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /mcL
Platelets	≥ 100,000 / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculateda creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for subject 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 liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN ≤ 1.5 X ULN
[a] Creatinine clearance should be calculated per institutional standard.	

7. Be a male, or a non-pregnant and non-breast feeding female; further:

   a. if female with reproductive potential: subject must demonstrate a serum β-human chorionic gonadotropin (β–hCG) level consistent with the nongravid state at the screening visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the screening visit, throughout the trial and until 120 days after the last dose of MK-3475 or until the last blood draw (for non-treatment controls). Acceptable methods of birth control are defined in Section 5.7.2.

   b. if postmenopausal female: subject is without menses for at least 1 year and have a documented follicle stimulating hormone (FSH) level in the postmenopausal range at screening,

   c. if a surgically sterile female: subject is status post hysterectomy, oophorectomy, or tubal ligation.

NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded, unless they demonstrate a serum β-human chorionic gonadotropin (β–hCG) level consistent with the nongravid state at the screening visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the screening visit, throughout the trial and until 120 days after the last dose of MK-3475 or until the last blood draw (for non-treatment controls). Information must be captured appropriately within the site's source documents

8. Male subjects with a female partner of childbearing potential should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy or until the last blood draw (for non-treatment controls). If their partner is pregnant, male subjects must agree to use a condom and no additional method of contraception is required for the pregnant partner. If their partner is of child-bearing potential, male subjects should use a condom with spermicide.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of screening.
2. Has a diagnosis of immunosuppression or has received systemic steroid therapy or any other form of immunosuppressive therapy within 4 weeks prior to screening.
3. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy for the treatment of RCC.
4. Has a known additional malignancy (other than RCC) that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and *in situ* cervical cancer that has undergone potentially curative therapy.
5. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. The presence of RCC metastases to other sites is permitted.
6. Has an active autoimmune disease or a documented history of autoimmune disease. Subjects with vitiligo or resolved childhood asthma/atopy are an exception to this rule. Subjects that require intermittent use of bronchodilators will not be excluded from the study.
7. Has a history of (non-infectious) pneumonitis that required treatment with steroids or current pneumonitis.
8. Has an active infection requiring systemic therapy.

9. Is receiving anticoagulant therapy or has received anticoagulant therapy within 10 days prior to screening. Certain platelet aggregation inhibitors are permitted (see Section 5.5.1 below)
10. Has severe cardiovascular disease, i.e. arrhythmias, requiring chronic treatment, congestive heart failure (NYHA Class III or IV) or symptomatic ischemic heart disease.
11. Has hepatic decompensation (Child-Pugh score > 6 [class B and C]).
12. Has uncontrolled thyroid dysfunction. Subjects with hypothyroidism stable on thyroid hormone replacement will not be excluded from the study.
13. Has uncontrolled diabetes mellitus.
14. 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.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected maximal duration of the trial, which would extend from the screening visit through 120 days after the last dose of study drug of MK-3475 or until the last blood draw (for non-treatment controls).
17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab) or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
18. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
19. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
20. Has received a live vaccine within 30 days prior to screening.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Biologic	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
MK-3475	200 mg	Q3 weeks	IV	2 (or up to 3*) doses	Experimental, Neoadjuvant
MK-3475	200 mg	Q3 weeks	IV	Up to 17 doses†	Experimental, Post-Resection
*Potential increase in number of doses will be based on interim analysis (see Section 8.0). †MK-3475 doses may be withheld due to toxicity, as described in Section 5.2.1.2.					

Trial Treatment should begin within 28 days of randomization or treatment assignment for those randomized to receive neoadjuvant MK-3475.

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/Modification

5.2.1.1 Dose Selection (Preparation)

For those subjects randomized to receive neoadjuvant treatment, MK-3475 (200 mg) will be administered intravenously Q3W for a total of two (or possibly three) doses. Two to three weeks following the final dose, patients should undergo SOC surgical resection of their RCC tumors.

Following recovery from surgical RCC resection, all subjects may receive MK-3475 (200 mg) administered intravenously Q3W for up to 17 doses (1 year of treatment).

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6 for neoadjuvant dosing and Table 3 for post-resection dosing.

5.2.1.2.1.1 Neoadjuvant MK-3475

Based on the first interim analysis of lymphocytic infiltrates in tumors resected from the first 9 subjects, if an increase in tumor lymphocytic infiltration of 2-fold or greater is not observed in more than one of the 6 subjects in this group that received a 2 dose course of neoadjuvant

MK-3475, all subsequent subjects enrolled in this trial may be treated with 3 doses of MK-3475. Details are described in Section 8.0 – Statistical Analysis Plan.

Administration of neoadjuvant MK-3475 during this trial must be discontinued for drug-related toxicities above Grade 1 in severity and for severe or life-threatening AEs as described in Section 5.6.1. Such subjects should proceed with SOC surgical RCC resection as soon as they have sufficiently recovered from the AE to undergo this procedure.

For subjects without metastatic disease at the time of surgical RCC resection who experience drug-related toxicities above Grade 1 during neoadjuvant treatment, post-resection MK-3475 should also not be administered and the subject should be permanently discontinued. However, subjects with known metastatic disease at the time of surgical RCC resection who develop Grade 2 or greater drug-related AEs during neoadjuvant MK-3475 treatment may still be eligible to receive post-resection MK-3475 if the drug-related AE severity as listed in Table 3 below does not prescribe permanent treatment discontinuation.

5.2.1.2.1.2 Post-Resection MK-3475

Post-resection administration of MK-3475 must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.2 for supportive care guidelines, including use of corticosteroids to be followed during post-resection administration of MK-3475 (only applicable in the Post-Resection Phase of the study).

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab (During Post-Resection Phase ONLY)

General instructions:

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

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

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

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

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

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

5.2.2 Timing of Dose Administration

MK-3475 solution for intravenous administration will be prepared and dosed per the instructions outlined in the Pharmacy Manual.

MK-3475 will be administered as a 30 minute IV infusion every 3 weeks (Q3W). The study site(s) 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 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Trial treatment should be administered following the schedule in Section 6.0 and after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Unless otherwise specified, trial treatment may be administered up to 3 days before or after the scheduled day of each cycle for administrative reasons.

All trial treatments will be administered on an outpatient basis.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects will be assigned randomly according to a computer-generated allocation schedule.

The sample allocation schedule is shown in Table 4.

Table 4 Sample Allocation Schedule

Patients[a]	Treatment Group
n=24	200 mg MK-3475 Q3 weeks, 2 or 3 doses[b]
n=12	Control

[a] Patients will be randomized to receive neoadjuvant MK-3475 or control. Allocation will be done in blocks of 3, ensuring 6 treated and 3 controls will be available for the first interim analysis. Depending on results of the first interim analysis, the control arm (and allocation numbers associated with the control arm) may be dropped from the allocation schedule, in which case patient numbers will be 33 and 3 for MK-3475 and controls, respectively.

[b] Also depending on the results of the first interim analysis, the number of neoadjuvant doses of MK-3475 may be increased from 2 to 3.

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)

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of receiving the first dose of MK-3475, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or allocation) must first be discussed between the investigator and Sponsor Clinical Director prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor Clinical Director can consult. The subject will be allowed to continue in the trial if both the Sponsor Clinical Director and the investigator agree.

5.5.1 Acceptable Concomitant Medications

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 concomitant medications received within 28 days before screening and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the investigator or the Sponsor Clinical Director.

Subjects receiving therapy with NSAIDS are permitted to continue this medication throughout the study, as clinically indicated. Subjects receiving other platelet aggregation inhibitors (e.g. Clopidogrel) may continue such medications, provided they are held for at least 5 days prior to pretreatment tumor biopsy and prior to surgical RCC resection, and are not restarted until at least the day following the procedure.

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

Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phases of this trial:

- Anti-cancer systemic chemotherapy or biological therapy, other than the study prescribed administration of MK-3475
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy

  Note: Radiation therapy to a symptomatic lesion or to the brain may be considered on a case-by-case basis after consultation with the Sponsor. Such a radiated lesion should not be a RECIST 1.1 target lesion.

- Live vaccines within 30 days prior to screening and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids, for any purpose other than to modulate AEs of suspected immunologic etiology or on the day of surgical RCC resection to modulate perioperative nausea.

  Note: If systemic glucocorticoids are administered to a subject receiving MK-3475 during the neoadjuvant phase of the trial to modulate an AE of suspected immunologic etiology, the guidance in Section 5.2.1.2.1.1 should be followed with regard to continued MK-3475 administration.

- Anticoagulants, other than those administered by subcutaneous injection for deep vein thrombosis (DVT) prophylaxis in the perioperative and postoperative period. Prohibited anticoagulants include, but are not limited to heparin (iv), enoxaparin, and warfarin. Note: platelet aggregation inhibitors are permitted with certain restrictions (See Section 5.5.1).

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

Upon completion of the first visit in the follow-up phase of the trial (See Section 6- Trial Flow Chart), there are no prohibited therapies.

5.6 Rescue Medications & Supportive Care

All AEs are to be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (http://ctep.cancer.gov).

NOTE: RESCUE MEDICATION AND SUPPORTIVE CARE GUIDELINES SIGNIFICANTLY DIFFER BETWEEN THE NEOADJUVANT AND POST-RESECTION PHASES OF THIS TRIAL.

5.6.1 Supportive Care Guidelines During the Neoadjuvant Portion of this Trial

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

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
    - In subjects with severe enterocolitis (Grade 3-4), neoadjuvant MK-3475 treatments will be discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In subjects with moderate enterocolitis (Grade 2), neoajduvant MK-3475 will be discontinued and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the Administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475 during the neoadjuvant phase of this study.

Table 5 Infusion Reaction Treatment Guidelines-**Neoadjuvant MK-3475 Only**

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 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 one 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 should be permanently discontinued from further neoadjuvant MK-3475 administration.**	No subsequent neoadjuvant MK-3475 dosing. Subject should proceed to SOC RCC resection. Only for subjects with known metastatic disease at the time of RCC resection: If post-resection MK-3475 is to be subsequently administered, subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

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: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 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. **Subject is permanently discontinued from further MK-33475 administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room 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		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest (ECIs) and Immune-Related Adverse Events (irAEs) During Neoadjuvant MK-3475 Only

Events of clinical interest of a potential immunologic etiology may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of MK-3475, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Subjects who develop a Grade 2 or higher irAEs should be discussed immediately with the Sponsor.

Recommendations for managing irAEs during the neoadjuvant phase of the trial that are not detailed elsewhere in the protocol are detailed in Table 6.

Table 6 General Approach to Handling irAEs- **Neoadjuvant Phase Only**

irAE	Discontinue study treatments?	Supportive Care
Grade 1	No action	Provide symptomatic treatment.
Grade 2	Discontinue neoadjuvant MK-3475 treatment.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3 and Grade 4	Discontinue neoadjuvant MK-3475 treatment.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis- Neoadjuvant MK-3475 Only

Subjects with symptomatic pneumonitis should immediately stop receiving treatments and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. For subjects who are determined to have study drug associated pneumonitis, the suggested treatment plan is outlined in Table 7.

Table 7 Recommended Approach for Handling Pneumonitis- Neoadjuvant Phase Only

Study Drug Associated Pneumonitis	Discontinue study treatments?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2, 3 and 4	Discontinue neoadjuvant MK-3475 treatment.	Systemic corticosteroids are indicated.

5.6.2 Supportive Care Guidelines During Post-Resection MK-3475 Treatment for this Trial

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 5.2.1.2, [Table 3]. 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 3] in Section 5.2.1.2 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.

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines-Post-Resection Phase Only

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 study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ 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 study drug treatment.**	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 situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

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

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as (1) surgically sterilized, or (2) postmenopausal (a woman who has not had menses for greater than 1 year will be considered postmenopausal (and this will be confirmed by FSH testing)),

or (3) not heterosexually active for the duration of the trial. The two birth control methods can consist of two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from the screening visit throughout the study period up to 120 days after the last dose of study drug or until the last blood draw (for non-treated controls).

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide, as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2.

If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-3475 is 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

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Discontinuation from treatment is "permanent". Once a subject is discontinued, he/she shall not be allowed to restart treatment.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- For subjects who have declined a study-prescribed pre-treatment core needle biopsy but instead have undergone a diagnostic biopsy performed as per local SOC from which tissue will be submitted, this biopsy was not performed within 45 days prior to the first dose of MK-3475 or tissue submitted is not sufficient for the specified study-related analyses.
- The subject, if randomized to receive neoadjuvant MK-3475, interrupts neoadjuvant trial medication administration for more than 7 consecutive days or 1 cumulative missed dose.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.
- The subject has a confirmed positive serum pregnancy test.
- In subjects assigned to receive neoadjuvant MK-3475, histologic analysis of the pre-treatment core needle biopsy does not confirm the diagnosis of RCC with one or more clear cell components present.
- In all subjects, histologic examination of the surgically excised tumor tissue does not confirm the diagnosis of RCC with clear cell elements.
- In subjects assigned to receive neoadjuvant MK-3475, the patient does not undergo surgical RCC resection within 5 weeks of the final dose of MK-3475.

- In subjects assigned to the control group (no neoadjuvant MK-3475), the patient fails to undergo surgical RCC resection within 6 weeks of randomization.
- The subject has not recovered from surgical RCC resection and therefore does not begin post-resection MK-3475 within 60 days of surgery.

  Note: Exception if Sponsor approves a longer interval between surgery and the start of post-resection MK-3475
- In subjects with metastatic disease at the time of RCC resection, radiologic disease progression is confirmed by local site assessment during post-resection MK-3475 administration.

  Note: Such subjects should be managed by irRECIST, with PD confirmed as outlined in Section 5.8.1.

  Note: Exception if Sponsor approves treatment continuation (Section 5.8.1)
- In subjects without metastatic disease at the time of RCC resection, metastatic or locally recurrent disease is confirmed by local site assessment during post-resection MK-3475 administration.

  Note: Exception if Sponsor approves treatment continuation (Section 5.8.1)
- Unacceptable adverse experiences as described in Section 5.2.1.2 Dose Modification.
- Intercurrent illness that prevents further administration of treatment.
- Investigator decides to withdraw the subject.
- Noncompliance with trial treatment or procedure requirements.
- The subject is lost to follow-up.
- The subject has completed 17 administrations (approximately 1 year) of post-resection MK-3475 treatment.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). For those subjects receiving MK-3475, following the final dose of study drug, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of MK-3475 treatment as described in Section 7.2.3.1).

Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for OS until death, withdrawal of consent, or the end of the trial, whichever occurs first.

5.8.1 Treatment after Initial Radiologic Progression (irRECIST-based Management)

Note: irRECIST-based management is ONLY applicable in cases where metastatic RCC was identified pre-operatively and the subject is receiving post-resection MK-3475.

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 can manifest as a clinical response after an initial apparent increase in tumor burden (i.e., pseudoprogression) or even the appearance of new lesions. Standard RECIST-based assessment of disease progression may, thus, not provide an accurate assessment of response to immunotherapeutic agents such as pembrolizumab. For this reason, irRECIST has been developed to help guide treatment decisions during tumor immunotherapy.

For subjects who have initial radiological evidence of radiological PD by RECIST 1.1 as determined by the site, the investigator may elect to continue a subject on study treatment until repeat imaging is obtained (irRECIST-based management) (see Table 9). This clinical judgment decision by the investigator should only be made if the subject is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. Such subjects may continue to receive study treatment and a imaging-based tumor assessment should be repeated ≥ 4 weeks later in order to reassess PD per investigator assessment.

Clinical stability is defined by the following:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values,
- No decline in ECOG performance status,
- Absence of rapid progression of disease, AND
- Absence of tumor progression at critical anatomical sites that requires urgent alternative medical intervention (e.g., CNS metastasis with potential for cord compression)

NOTE: Subjects exhibiting toxicity from trial therapy as outlined in Section 5.2.1.2 and 7.2 may NOT continue to receive trial therapy.

NOTE: Any subject deemed **clinically unstable** should be discontinued from trial treatment at investigator-assessed 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

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

Upon repeat imaging, PD will be confirmed if ANY of the following occur by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is worse (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is worse (qualitative assessment)
- 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 trial therapy (exception noted below in this Section 5.8.1).

Upon repeat imaging, PD will have failed to be confirmed if ALL of the following occur by irRECIST:

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

If repeat local site imaging fails to confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

When feasible, subjects should not be discontinued until after PD 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 who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flares include any of the following scenarios:

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

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

Table 9 Imaging and Treatment after First Radiologic Evidence of PD (irRESIST-based Management) (Post-Resection MK-3475 Only)

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	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

5.9 Subject Replacement Strategy

If a subject discontinues from the trial, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique randomization number. The trial site should contact the Sponsor for the replacement subject's randomization number.

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, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be appraised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart - Patients Randomized to Neoadjuvant MK-3475

Trial Period:	Screening	Randomization[a]	Pretreatment Core Biopsy	MK-3475		SOC Tumor Resection	Post-operative Follow Up
Week:	-2	-2	-1	1	4	7	12[b]
Scheduling window (days)	±14	±14	±6	±3	±3	-7/+14	-5/+7
Administrative Procedures							
Informed Consent[c]	X						
Informed Consent for Future Biomedical Research[d]	X						
Inclusion/Exclusion Criteria	X						
Subject Identification Card	X						
Medical History	X						
ECOG Performance Scale Assessment	X						
Concomitant Medication Review[e]	X		X	X	X	X	X
Clinic Procedures/Assessments							
Full Physical Examination[f]	X			X	X		
Directed Physical Examination[f]						X[g]	X
Vital Signs, Weight and Height[h]	X			X	X	X[g]	X
12-Lead Electrocardiogram (performed locally)	X[i]	as clinically indicated					
Tumor Core Needle Biopsy[j]			X[k]			X[l]	
MK-3475 Administration[m]				X	X		
SOC Tumor Resection						X	
Adverse Events Monitoring[n]	X		X	X	X	X	X
Assessment of Surgical Complications							X[o]
Laboratory Procedures/Assessments							
Pregnancy Test- Urine or Serum β-HCG or FSH[p]	X[i]			X			
PT/INR and aPTT	X[i]					X[q,r]	X
CBC with Differential	X[i]			X	X	X[q]	X
Chemistry	X[i]			X	X	X[q]	X
Urinalysis	X[i]						
T3, FT4, and TSH	X[i]				X		X
Blood for HLA typing			X[s,t]				
HIV/Hepatitis Screen	X[i]						

Trial Period:		Screening	Randomization[a]	Pretreatment Core Biopsy	MK-3475		SOC Tumor Resection	Post-operative Follow Up
	Week:	-2	-2	-1	1	4	7	12[b]
	Scheduling window (days)	±14	±14	±6	±3	±3	-7/+14	-5/+7
Protocol-Specific Specimen Collection								
Tissue Collection	Fresh tumor tissue for shipping (TIL analysis, histoculture, tumor cell isolation and IMR expression analysis)						X	
	Tumor tissue for FFPE (IHC; DNA for mutational analysis, TCR utilization, promoter methylation analysis; RNA for gene expression and miRNA analysis)			X[u]			X[v,w]	
	Fresh tumor tissue for snap freezing (DNA isolation, metabolic profiling, laser capture microdissection)						X	
	Fresh non-malignant kidney tissue from resected tumor specimen for snap freezing (DNA isolation)						X	
	Fresh tumor tissue in RNAlater solution (RNA extraction, gene expression)						X	
	Fresh non-malignant kidney tissue in RNAlater solution (RNA extraction, gene expression)						X	
Blood	PBMC Phenotypic Analysis			X[t]			X[q]	X
	PBMC Isolation and Cryopreservation (Antigen-specific T cell response evaluation)			X[t]			X[q]	X
	Plasma (miRNA, and exosome evaluation)			X[t]			X[q]	X
	Serum (biomarkers)			X[t]			X[q]	X
	Serum (PK/PD)				X[x]	X[y]	X[q]	X
	RNA isolation (gene expression, miRNA expression)			X[t]			X[q]	X
	DNA isolation (TCR utilization)[z]			X[t]			X[q]	X
	B cell isolation and transformation							
Urine for exosome isolation and analysis				X[t]			X[aa]	X

a. Randomization, initially 2:1 neoadjuvant MK-3475:controls. Randomization will occur only after written consent is obtained and will occur after all screening assessments have been completed. Randomization can occur at any time point after screening and prior to core biopsy.
b. This follow up visit must occur no less than 30 days after the day of SOC tumor resection.
c. Written consent must be obtained prior to performing any protocol-specific procedure. 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 28 days prior to screening.
d. If the subject signs the FBR consent, leftover samples may be kept for Future Biomedical Research.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through 30 days after the last dose of trial treatment. Record all medications taken for SAEs as defined in Section 7.2
f. Full PE at screening and neoadjuvant MK-3475 treatment visits; Directed PE for all other visits.
g. These procedures may be performed up to 36 hours prior to the start of the SOC RCC tumor resection surgical procedure.
h. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening visit only. Vital signs will be collected at screening, prior to the administration of each dose of trial treatment, at SOC tumor resection, and at post-operative follow-up.
i. Laboratory tests for screening are to be performed within 28 days prior to the first dose of trial treatment. See section 7.1.3 for details regarding laboratory testing.
j. If a diagnostic biopsy has already been performed per local SOC and sufficient tissue from that sample is available and will be submitted for all study-related analyses specified for the preoperative biopsy tissue, the study-specified pretreatment biopsy will not be required and these assessments should be performed on the day that pretreatment blood and urine samples (see footnote t below) are collected.
k. Percutaneous core needle biopsy of RCC performed under image guidance. This procedure may take place any time between randomization to the MK-3475 treatment group and the start of treatment with MK-3475. This study-prescribed pretreatment core needle biopsy is not required if a diagnostic biopsy has been performed per local SOC for diagnostic purposes, this biopsy will have been performed within 45 days prior to the first dose of MK-3475, and sufficient tissue is available from such a specimen for all study-related analyses specified for the pretreatment biopsy.
l. During the surgical procedure and prior to cross-clamping of the renal artery, under direct vision a core needle biopsy of the RCC may be performed at the discretion of the operating surgeon and subject to local IRB approval.
m. The number of doses of MK-3475 may be increased to three doses, based on the results of the first interim analysis, as described in Section 8.0 (See Table 12 for the flow chart should this occur).
n. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
o. At this visit, the occurrence of any surgical complications within 30 days of the operative procedure will specifically be assessed.
p. For female subjects of reproductive potential, a urine pregnancy test should be performed within 72 hours of the first dose of trial treatment. If urine pregnancy results 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. For women thought to be post-menopausal, serum FSH will be measured to confirm post-menopausal status.
q. Blood for study related analyses may be collected at any time prior to surgery on the day of surgery. Ideally these blood samples will be collected via the iv cannula placed in preparation for surgery, but these samples may also be collected via venipuncture earlier on the day of surgery, at the discretion of the clinical care team
r. Blood for assessment of these coagulation parameters may be drawn up to 72 hours before the day of SOC tumor resection, at the discretion of the operative team. If such a sample is collected, a sample for these tests will not need to be collected on the day of surgery.
s. Low resolution HLA-A and B typing, to be performed by local HLA typing laboratory.
t. Blood and urine samples should be collected on the day of the pretreatment core biopsy, However, if tissue from a biopsy previously performed per local SOC for diagnostic purposes will be submitted for all specified study-related analyses, these blood and urine samples should be collected as close to the time of this biopsy as possible and must be collected prior to the first dose of MK-3475.

u. A minimum of 3 18-gauge core biopsy tumor samples will be collected. The harvested cores will be placed in single cassette for formalin fixation and paraffin embedding. The entire specimen will then be cut onto slides. After the diagnosis of RCC is confirmed by the local site pathologist, the remaining tissue sections will be used for study related analyses.
v. A minimum of 3 18-gauge core biopsy tumor samples may be collected intraoperatively under direct vision by the surgeon prior to cross-clamping of the renal artery on the side of the RCC. The harvested cores will be placed in single cassette for formalin fixation and paraffin embedding. The FFPE block will then be shipped to Central Laboratory.
w. Following tumor resection, additional tumor tissue will be collected for formalin fixation and paraffin embedding. These FFPE blocks will then be shipped to Central Laboratory.
x. Blood sample to be collected 30 minutes after the completion of MK-3475 dosing.
y. Blood samples to be collected immediately prior to and 30 minutes after the completion of MK-3475 dosing.
z. Any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
aa. Urine will be collected prior to surgery on the day of the surgical RCC resection.

6.2 Trial Flow Chart - Patients Randomized to No Treatment Control Group

Trial Period:	Screening	Randomization[a]	SOC Tumor Resection	Post-Operative Follow-up
Week	-2	-2	1	6[b]
Scheduling window (days)	±14	±14	±14	-5/+7
Administrative Procedures				
Informed Consent[c]	X			
Informed Consent for Future Biomedical Research[d]	X			
Inclusion/Exclusion Criteria	X			
Subject Identification Card	X			
Medical History	X			
ECOG Performance Scale Assessment	X			
Concomitant Medication Review[e]	X		X	X
Clinic Procedures/Assessments				
Full Physical Examination[f]	X			
Directed Physical Examination[f]			X[g]	X
Vital Signs, Weight and Height[h]	X		X[g]	X
12-Lead Electrocardiogram (performed locally)	X[i]		As clinically indicated	
SOC Tumor Resection			X	
Tumor Core Needle Biopsy[j]			X[j]	
Adverse Events Monitoring[k]	X		X	X
Assessment of Surgical Complications				X[l]
Laboratory Procedures/Assessments				
Pregnancy Test- Urine or Serum β-HCG or FSH[m]	X[i]			X
PT/INR and aPTT	X[i]		X[n,o]	X
CBC with Differential	X[i]		X[n]	X
Chemistry	X[i]		X[n]	X
Urinalysis	X[i]			
T3, FT4, and TSH	X[i]			
Blood for HLA typing			X[n,p]	
HIV/Hepatitis Screen	X[i]			

Trial Period:		Screening	Randomization[a]	SOC Tumor Resection	Post-Operative Follow-up
	Week	-2	-2	1	6[b]
	Scheduling window (days)	±14	±14	±14	-5/+7
Protocol-Specific Specimen Collection					
Tissue Collection	Fresh tumor tissue for shipping (TIL analysis, histoculture, tumor cell isolation and IMR expression analysis)			X	
	Tumor tissue for FFPE (IHC; DNA for mutational analysis, TCR utilization, promoter methylation analysis; RNA for gene expression and miRNA analysis)			X[q,r]	
	Fresh tumor tissue for snap freezing (DNA isolation, metabolic profiling, laser capture microdissection)			X	
	Fresh non-malignant kidney tissue from resected tumor specimen for snap freezing (DNA isolation)			X	
	Fresh tumor tissue in RNAlater solution (RNA extraction, gene expression)			X	
	Fresh non-malignant kidney tissue in RNAlater solution (RNA extraction, gene expression)			X	
Blood	PBMC Phenotypic Analysis			X[m]	X
	PBMC Isolation and Cryopreservation (Antigen-specific T cell response evaluation)			X[m]	X
	Plasma (miRNA, and exosome evaluation)			X[m]	X
	Serum (biomarkers)			X[m]	X
	Blood for RNA isolation (gene expression, miRNA expression)			X[m]	X
	Blood for DNA isolation (TCR utilization)[s]			X[m]	X
Urine for exosome isolation and analysis				X[t]	X

a. Randomization, initially 2:1 neoadjuvant MK-3475:controls. Randomization will occur only after written consent is obtained and will occur after all screening assessments have been completed.
b. This follow up visit must occur no less than 30 days after the day of SOC tumor resection.
c. Written consent must be obtained prior to performing any protocol-specific procedure. 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 28 days prior to screening.
d. If the subject signs the FBR consent, leftover samples may be kept for Future Biomedical Research.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2
f. Full PE at screening visit; Directed PE for all other visits.
g. These procedures may be performed up to 36 hours prior to the start of the SOC RCC tumor resection surgical procedure.
h. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening visit only. Vital signs will be collected at screening, prior to the administration of each dose of trial treatment, at SOC tumor resection, and at post-operative follow-up.
i. Laboratory tests for screening are to be performed prior to randomization. See section 7.1.3 for details regarding laboratory testing.
j. During the surgical procedure and prior to cross-clamping of the renal artery, under direct vision a core needle biopsy of the RCC may be performed at the discretion of the operating surgeon and subject to local IRB approval.
k. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
l. At this visit, the occurrence of any surgical complications within 30 days of the operative procedure will specifically be assessed.
m. For female subjects of reproductive potential, 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. For women thought to be post-menopausal, serum FSH will be measured to confirm post-menopausal status.
n. Blood for study related analyses may be collected at any time prior to surgery on the day of surgery. Ideally these blood samples will be collected via the iv cannula placed in preparation for surgery, but these samples may also be collected via venipuncture earlier on the day of surgery, at the discretion of the clinical care team.
o. Blood for assessment of these coagulation parameters may be drawn up to 72 hours before the day of SOC tumor resection, at the discretion of the operative team. If such a sample is collected, a sample for these tests will not need to be collected on the day of surgery.
p. Low resolution HLA-A and B typing, to be performed by local HLA typing laboratory.
q. A minimum of 3 18-gauge core biopsy tumor samples may be collected intraoperatively under direct vision by the surgeon prior to cross-clamping of the renal artery on the side of the RCC (see footnote h). The harvested cores will be placed in single cassette for formalin fixation and paraffin embedding. The FFPE block will then be shipped to Central Laboratory for further processing and analysis.
r. Following tumor resection, additional tumor tissue will be collected for formalin fixation and paraffin embedding. These FFPE blocks will then be shipped to Central Laboratory.
s. Any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
t. Urine will be collected prior to surgery on the day of the surgical RCC resection.

6.3 Trial Flow Chart - Patients Randomized to Neoadjuvant MK-3475 (3 DOSE REGIMEN)

Trial Period:	Screening	Randomization[a]	Pretreatment Core Biopsy	MK-3475			SOC Tumor Resection	Post-Operative Follow-up
Week:	-2	-2	-1	1	4	7	10	15[b]
Scheduling window (days)	±14	±14	±6	±3	±3	±3	-7/+14	-5/+7
Administrative Procedures								
Informed Consent[c]	X							
Informed Consent for Future Biomedical Research[d]	X							
Inclusion/Exclusion Criteria	X							
Subject Identification Card	X							
Medical History	X							
ECOG Performance Scale Assessment	X							
Concomitant Medication Review[e]	X		X	X	X	X	X	X
Clinic Procedures/Assessments								
Full Physical Examination[f]	X			X	X	X		
Directed Physical Examination[f]							X[g]	X
Vital Signs. Weight and Height[h]	X			X	X	X	X[g]	X
12-Lead Electrocardiogram (performed locally)	X[i]	as clinically indicated						
Tumor Core Needle Biopsy[j]			X[k]				X[l]	
MK-3475 Administration[m]				X	X	X		
SOC Tumor Resection							X	
Adverse Events Monitoring[n]	X		X	X	X	X	X	X
Assessment of Surgical Complications								X[o]
Laboratory Procedures/Assessments								
Pregnancy Test- Urine or Serum β-HCG or FSH[p]	X[i]			X				
PT/INR and aPTT	X[i]						X[q,r]	X
CBC with Differential	X[i]			X	X	X	X[q]	X
Chemistry	X[i]			X	X	X	X[q]	X
Urinalysis	X[i]							
T3, FT4, and TSH	X[i]				X			X
Blood for HLA typing			X[s,t]					
HIV/Hepatitis Screen	X[i]							

Trial Period:		Screening	Randomization[a]	Pretreatment Core Biopsy	MK-3475			SOC Tumor Resection	Post-Operative Follow-up
Week:		-2	-2	-1	1	4	7	10	15[b]
Scheduling window (days)		±14	±14	±6	±3	±3	±3	-7/+14	-5/+7
Protocol-Specific Specimen Collection									
Tissue Collection	Fresh tumor tissue for shipping (TIL analysis, histoculture, tumor cell isolation and IMR expression analysis)							X	
	Tumor tissue for FFPE (IHC; DNA for mutational analysis, TCR utilization, promoter methylation analysis; RNA for gene expression and miRNA analysis)			X[u]				X[v,w]	
	Fresh tumor tissue for snap freezing (DNA isolation, metabolic profiling, laser capture microdissection)							X	
	Fresh non-malignant kidney tissue from resected tumor specimen for snap freezing (DNA isolation)							X	
	Fresh tumor tissue in RNAlater solution (RNA extraction, gene expression)							X	
	Fresh non-malignant kidney tissue in RNAlater solution (RNA extraction, gene expression)							X	
Blood	PBMC Phenotypic Analysis			X[t]				X[q]	X
	PBMC Isolation and Cryopreservation (Antigen-specific T cell response evaluation)			X[t]				X[q]	X
	Plasma (miRNA, and exosome evaluation)			X[t]				X[q]	X
	Serum (biomarkers)			X[t]				X[q]	X
	Serum (PK/PD)				X[x]		X[y]	X[q]	X
	RNA isolation (gene expression, miRNA expression)			X[t]				X[q]	X
	DNA isolation (TCR utilization)[z]			X[t]				X[q]	X
	B cell isolation and transformation								
Urine for exosome isolation and analysis				X[t]				X[aa]	X

a. Randomization, initially 2:1 neoadjuvant MK-3475:controls. Randomization will occur only after written consent is obtained and will occur after all screening assessments have been completed. Randomization can occur at any time point after screening and prior to core biopsy.
b. This follow up visit must occur no less than 30 days after the day of SOC tumor resection.
c. Written consent must be obtained prior to performing any protocol-specific procedure. 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 28 days prior to screening.
d. If the subject signs the FBR consent, leftover samples may be kept for Future Biomedical Research.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through 30 days after the last dose of trial treatment. Record all medications taken for SAEs as defined in Section 7.2
f. Full PE at screening and neoadjuvant MK-3475 treatment visits; Direct PE for all other visits.
g. These procedures may be performed up to 36 hours prior to the start of the SOC RCC tumor resection surgical procedure.
h. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening visit only. Vital signs will be collected at screening, prior to the administration of each dose of trial treatment, at SOC tumor resection, and at post-operative follow-up.
i. Laboratory tests for screening are to be performed within 28 days prior to the first dose of trial treatment. See section 7.1.3 for details regarding laboratory testing.
j. If a diagnostic biopsy has already been performed per local SOC and sufficient tissue from that sample is available and will be submitted for all study-related analyses specified for the preoperative biopsy tissue, the study-specified pretreatment biopsy will not be required, and these assessments should be performed on the day that pretreatment blood and urine samples (see footnote w below) are collected.
k. Percutaneous core needle biopsy of RCC performed under image guidance. This procedure may take place any time between randomization to the MK-3475 treatment group and the start of treatment with MK-3475. This study-prescribed pretreatment core needle biopsy is not required if a diagnostic biopsy has been performed per local SOC for diagnostic purposes, this biopsy will have been performed within 45 days prior to the first dose of MK-3475, and sufficient tissue is available from such a specimen for all study-related analyses specified for the pretreatment biopsy.
l. During the surgical procedure and prior to cross-clamping of the renal artery, under direct vision a core needle biopsy of the RCC may be performed at the discretion of the operating surgeon and subject to local IRB approval.
m. The number of doses of MK-3475 may be increased to three doses, based on the results of the first interim analysis, as described in Section 8.0 (See Table 9 for the flow chart should this occur).
n. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
o. At this visit, the occurrence of any surgical complications within 30 days of the operative procedure will specifically be assessed.
p. For female subjects of reproductive potential, a urine pregnancy test should be performed within 72 hours of the first dose of trial treatment. If urine pregnancy results 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. For women thought to be post-menopausal, serum FSH will be measured to confirm post-menopausal status.
q. Blood for study related analyses may be collected at any time prior to surgery on the day of surgery. Ideally these blood samples will be collected via the iv cannula placed in preparation for surgery, but these samples may also be collected via venipuncture earlier on the day of surgery, at the discretion of the clinical care team.
r. Blood for assessment of these coagulation parameters may be drawn up to 72 hours before the day of SOC tumor resection, at the discretion of the operative team. If such a sample is collected, a sample for these tests will not need to be collected on the day of surgery.
s. Low resolution HLA-A and B typing, to be performed by local HLA typing laboratory.
t. Blood and urine samples should be collected on the day of the pretreatment core biopsy, However, if tissue from a biopsy previously performed per local SOC for diagnostic purposes will be submitted for all specified study-related analyses, these blood and urine samples should be collected as close to the time of this biopsy as possible and must be collected prior to the first dose of MK-3475.

u. A minimum of 3 18-gauge core biopsy tumor samples will be collected. The harvested cores will be placed in single cassette for formalin fixation and paraffin embedding. The entire specimen will then be cut onto slides. After the diagnosis of RCC is confirmed by the local site pathologist, the remaining tissue sections will be used for study related analyses.
v. A minimum of 3 18-gauge core biopsy tumor samples may be collected intraoperatively under direct vision by the surgeon prior to cross-clamping of the renal artery on the side of the RCC. The harvested cores will be placed in single cassette for formalin fixation and paraffin embedding. The FFPE block will then be shipped to Central Laboratory.
w. Following tumor resection, additional tumor tissue will be collected for formalin fixation and paraffin embedding. These FFPE blocks will then be shipped to Central Laboratory.
x. Blood sample to be collected 30 minutes after the completion of MK-3475 dosing.
y. Blood samples to be collected immediately prior to and 30 minutes after the completion of MK-3475 dosing.
z. Any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
aa. Urine will be collected prior to surgery on the day of the surgical RCC resection.

6.4 Trial Flow Chart – Post-Resection MK-3475 Treatment (All Subjects)

Treatment Period:	Post-Resection MK-3475 (3-Week Cycles)				End of Treatment or Discontinuation Visit[c]	Post-Treatment	
						30 Day Follow-up	90 Day Phone Call
Treatment Week:	1[a]	4	7	Q3W[b]	52	30 days after last dose of treatment[c]	90 days after last dose of treatment
Scheduling Window (days):	+3	± 3	± 3	± 3	± 3	(±3)	(+7)
Clinical Procedures/Assessments							
MK-3475 Administration	X	X		X	X		
Adverse Events Monitoring[d]	X	X		X	X	X	X
Concomitant Medication Review	X	X		X	X	X	X
Laboratory Procedures/Assessments							
Pregnancy Test-Urine β-HCG	X[e]					X	
T3, FT4, and TSH	X		X	X[f]	X		
Laboratory Studies	**Laboratory studies should be performed at the discretion of the treating physician.**						
PBMC Isolation and Cryopreservation (Antigen-specific T cell response evaluation)			X				
Efficacy Measurements							
Tumor imaging	X[g]	**Additional tumor imaging at the discretion of the treating physician[h]**					

a. Post-resection MK-3475 administration should begin within 45 days (±15 days) following surgical RCC resection, but only after the Post-operative Follow-Up visit in Table 6.1, 6.2, or 6.3, and the subject has fully recovered from the surgical procedure.
b. MK-3475 200 mg IV Q3W can be continued for up to 17 treatment cycles (1 year of treatment).
c. If the Discontinuation visit occurs approximately 30 days from last dose of treatment, the same procedures do not need to be repeated for the 30 Day Follow-up visit.
d. Record all AEs occurring within 30 days after the last dose of MK-3475. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of MK-3475 or the start of new anti-cancer treatment, whichever comes first.
e. For female subjects of reproductive potential, a urine pregnancy test should 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 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.
f. Thyroid function testing (T3, FT4, and TSH) should be repeated every 6 weeks/every other cycle during post-resection treatment with MK-3475.
g. Optional tumor imaging should ideally be performed prior to the start of post-resection MK-3475. For patients with known metastatic disease at the time of RCC resection, this imaging should be performed at least 30 days following surgery but before the first dose of post-resection MK-3475.
h. The treating physician should obtain additional SOC tumor imaging studies as clinically indicated. For subjects with known metastatic disease at the time of RCC resection, local assessment of response should be assessed by the investigator using either RECIST v1.1 or irRECIST.

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.

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 sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial (See Sections 5.1.2 and 5.1.3).

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.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

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, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. See Section 5.5 for a description of allowed and prohibited medications.

7.1.1.6 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 allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a 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 randomization number.

7.1.1.8 Trial Compliance (Medication)

Interruptions from the protocol specified neoadjuvant MK-3475 treatment require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.7). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document in the Administrative Binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during screening, at Day 1 of each cycle, as specified in Section 6.0 – Trial Flow Charts. Clinically significant abnormal findings should be recorded as medical history. After the ICF is signed, new clinically significant abnormal physical examination findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam as per Section 6.0 – Trial Flow Charts and as clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Weight will be recorded as specified in the Trial Flow Chart. Height will be measured at screening only.

7.1.2.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures at Screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points for standard 12-lead ECGs will be performed as per Section 6.0 – Trial Flow Charts. Clinically significant abnormal findings seen on the follow-up ECGs should be recorded as adverse events.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 12.7) at screening.

7.1.2.6 Tumor Imaging and Assessment of Disease

The report from the clinical imaging study used to establish the diagnosis of RCC will be collected and reviewed at Screening. The images from these studies may be requested and collected and stored for possible further analysis. For any subsequent clinical imaging studies performed as part of SOC therapy through the study period, reports will be collected and reviewed, and images may be requested and stored for possible further analysis. No study-specified tumor imaging studies will be performed.

7.1.2.7 Assessment of Disease

RECIST 1.1 will be applied by the site as the primary measure for assessment of tumor response in those subjects with metastatic RCC at the time of surgical resection who then receive post-resection MK-3475 in this trial.

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 Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum/urine β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	Hepatitis
Platelet count	Alanine aminotransferase (ALT)	Protein	HIV
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	HLA-typing
	Bicarbonate	Microscopic exam, if abnormal results are noted	T3, FT4, TSH
	Calcium		PT/INR, aPTT
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen/ Blood Urea		

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma and/or urine samples collected, if any, will be assayed for evaluation of PK/PD will be collaboratively determined by the Departments of Pharmacokinetics, Pharmacodynamics & Drug Metabolism and the appropriate department within Early-Stage Development. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers.

7.1.3.2.1 Protocol Specific Specimen Collection

7.1.3.2.1.1 Tumor Tissue Collection

Pretreatment image-guided percutaneous core needle tumor biopsy (patient randomized to receive neoadjuvant MK-3475) for FFPE (RCC diagnosis confirmation, TIL analysis by IHC, DNA for TIL analysis, RNA for gene profiling). A study-prescribed pretreatment core needle biopsy is not required if a diagnostic biopsy has already been performed per local SOC, this biopsy has been performed within 45 days prior to the first dose of MK-3475, and sufficient tissue is available from such a biopsy for the study-related analyses specified for the pretreatment biopsy.

Intraoperative core needle tumor biopsy under direct vision (all patients) for FFPE (TIL analysis by IHC, DNA for TIL analysis, RNA for gene profiling), prior to renal artery cross-clamping, at the discretion of the operating surgeon, and subject to approval by the site IRB

Fresh resected tumor tissue (TIL analysis, histoculture, tumor cell isolation and IMR expression analysis): 10 cm^3 consisting of non-necrotic tumor tissue in approximately 1 cm^3 pieces, shipped fresh to Merck Research Laboratories. These tumor tissue pieces do not need to be contiguous within the tumor.

[redacted]

Resected non-malignant kidney tissue for DNA isolation (mutational analysis-negative control): one piece of tissue, approximately 0.5 cm x 0.5 cm x 0.5 cm in size, snap frozen; and one piece of tissue, approximately 0.5 cm x 0.5 cm x 0.5 cm in size, in RNAlater solution

Resected tumor tissue for storage in RNAlater solution (RNA for gene expression analysis, miRNA analysis): one non-necrotic piece of tumor tissue, approximately 0.5 cm x 0.5 cm x 0.5 cm in size

Resected non-malignant kidney tissue for DNA isolation (mutational analysis-negative control): one piece of tissue, approximately 0.5 cm x 0.5 cm x 0.5 cm in size, snap frozen

7.1.3.2.1.2 Blood Collection

Whole blood (PBMC phenotypic analysis)

Whole blood for PBMC isolation and cryopreservation (Antigen-specific T cell response evaluation)

Plasma (miRNA, exosome evaluation, other biomarkers)

Serum (protein evaluation, PK/PD measurements, other biomarkers)

Blood for RNA isolation (gene expression, miRNA expression)

Blood for DNA isolation (TCR utilization, promoter methylation)

Blood for B cell isolation and transformation

7.1.3.2.1.3 Urine Collection

Urine for exosome isolation and analysis

7.1.3.3 Future Biomedical Research

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

- Any leftover samples collected as part of the main study, including leftover DNA

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, at the time of discontinuation or as soon as possible after discontinuation depending upon the phase the subject is in, the subject may be asked to return to the clinic (or be contacted) for a discontinuation visit as outlined for Post-operative Follow Up visit or Discontinuation visit/30 Day Follow-up in Section 6.0 – Trial Flow Charts to have the applicable procedures conducted. The investigator should perform a follow-up phone call 90 days after the last dose of trial drug to determine if any SAEs/ECIs have occurred since the discontinuation visit. Any AEs 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.

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 Domiciling

Subjects will report to the clinical research unit (CRU) on the scheduled day of trial drug administration and remain in the unit until 2 hours post-dose on that day in each treatment period. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 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:

ECG equipment

Equipment to measure vital signs

Infusion pumps

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

Up to 2 weeks prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor. Any rescreening will be based on the medical judgment of the investigator, depending on patient status and risk-benefit assessment of delayed surgery versus administration of neoadjuvant MK-3475 therapy, in consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol specific procedure. 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 28 days prior to screening, except for the following:

- For women of reproductive potential, a repeat pregnancy test utilizing urine will be performed within 72 hours prior to first dose of trial treatment, if randomized to receive neoadjuvant MK-3475.

- For women of reproductive potential, a repeat pregnancy test utilizing urine will be performed within 72 hours prior to first dose of post-resection MK-3475.

7.1.5.2 Image-guided Percutaneous Tumor Core Needle Biopsy

Patients randomized to receive neoadjuvant MK-3475 will undergo image-guided percutaneous core needle biopsy of their RCC tumor prior to the first dose of MK-3475. The selection of the image modality for guiding the biopsy will be at the discretion of the study site investigator, based on local SOC, and will be performed in an outpatient setting. A minimum of 3 18-gauge biopsy cores of tissue will be collected. A study-prescribed pretreatment core needle biopsy is not required if a diagnostic biopsy has already been performed per local SOC, this biopsy will have been performed within 45 days prior to the first dose of MK-3475, and sufficient tissue is available from such a specimen for the study-related analyses specified for the pretreatment biopsy.

All of the collected cores from the study-prescribed biopsy will be paraffin embedded in a single cassette. The site pathologist and/or his/her designee will then section the entire tissue block (See Study Operations Manual). After the local pathologist confirms the diagnosis of RCC, all of the cut tissue sections not used to confirm the diagnosis of RCC will be shipped to the Sponsor's laboratory for further study-related analyses.

If tissue from a diagnostic biopsy performed per local SOC is to be submitted, slides cut from the single FFPE block containing a minimum of three 18-gauge biopsy cores (or an

equivalent volume of tumor tissue) will be shipped to the Sponsor's laboratory for further study-related analyses. Ideally, the entire FFPE block is sectioned and all slides submitted.

7.1.5.3 Neoadjuvant MK-3475 Treatment

Approximately one week following percutaneous tumor biopsy, patients randomized to receive neoadjuvant MK-3475 will begin receiving this agent. MK-3475 will be given every 3 weeks, for a total of 2 doses (which may be increased to 3 doses, as discussed in Section 8.0). Patients randomized to the control group will not receive any study drug or placebo and will bypass this neoadjuvant treatment period.

7.1.5.4 SOC Surgical RCC Resection

All patients enrolled in this trial will undergo SOC surgical excision of their RCC. For those patients randomized to receive neoadjuvant MK-3475, surgery should be performed approximately 2-3 weeks following the final dose of MK-3475. For patients randomized to the control group, surgery should be performed within 6 weeks of randomization. The decision to perform partial or complete nephrectomy and the surgical approach (open vs laparoscopic) will be left to the discretion of the operating surgeon.

In the operating room during the surgical procedure, an intraoperative core needle biopsy of the tumor may be performed under direct vision by the operating surgeon prior to cross-clamping of the renal artery. A minimum of three 18-gauge core biopsy tumor samples will be collected, fixed in formalin, and then placed in a single cassette for paraffin embedding. As discussed in Section 4.2.1.4 (subsection "Rationale for Intraoperative Core Needle Biopsies in this Trial"), the performance of this intraoperative RCC biopsy, which is critical for minimizing warm ischemia-induced potentially confounding changes in RCC gene expression, will be at the discretion of the operating surgeon and subject to approval by the study site IRB.

In the operating room, upon removal of the tumor from the patient, the surgeon or his/her designee will harvest and appropriately process the fresh tumor on the "back table." If the operating surgeon has not collected the intraoperative core needle tumor biopsy samples prior to renal artery crossclamping, core needle samples should be collected from the excised RCC tumor specimen on the back table in the operating room after the specimen has been removed from the patient and prior to further tumor specimen processing. Details regarding the tumor sample processing are included in the Study Operations Manual.

7.1.5.5 Follow-up After Surgical RCC Resection

All subjects will return to clinic approximately 5 weeks (30-42 days) following SOC surgical RCC resection for a routine postoperative visit, which will include assessment for AE occurrences and collection of blood and urine samples for study-related analyses. Assessment for surgical complications within the 30 day postoperative period will also be performed at this visit for all subjects.

7.1.5.6 Post-Resection MK-3475 Treatment

Following recovery from surgery, all subjects may receive post-resection MK-3475, 200 mg IV Q3W for up to 1 year.

Subjects with known metastatic RCC at the time of surgical resection ideally should undergo SOC radiologic tumor imaging prior to the start of post-resection MK-3475 administration. After the start of post-resection MK-3475, all subjects should be followed by SOC radiologic imaging to assess response to treatment at intervals to be selected by their treating physician. This physician should utilize RECIST 1.1 and/or irRECIST to assess response to MK-3475 and for making treatment decisions.

For all subjects, AEs should be monitored throughout the post-resection phase and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Treatment with post-resection MK-3475 may continue until documented disease progression or recurrence, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, consent withdrawn by subject, start of new anti-cancer treatment, subject lost to follow up, subject pregnancy, noncompliance with trial treatment or procedure requirements, completion of 17 cycles of post-resection MK-3475 (approximately 1 year of treatment), or discontinuation for administrative reasons.

7.1.5.7 Follow-up After Post-resection MK-3475 Treatment

For subjects who complete or discontinue early from post-resection MK-3475 treatment, safety follow up visit should be conducted approximately 30 days (± 3 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. SAEs and ECIs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Pregnancy status should be queried approximately 120 days after the end of treatment, and survival status 1 and 2 years following surgical tumor resection.

7.1.5.8 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the pretreatment percutaneous tumor biopsy in patients randomized to receive neoadjuvant MK-3475 is the critical procedure. This procedure must be performed at a minimum of one day before the first dose of MK-3475.

All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

7.1.5.9 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-3475 in humans, and the PK, PD and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data; and can include the following:

- Repeat of or decrease in the dose of the trial drug administered in any given period/panel
- Decrease in the duration of trial drug administration (e.g., number of days)
- Adjustment of the dosing interval (e.g., divided doses [BID to QD, QD to BID, TID or vice versa])

The PK/PD sampling scheme currently outlined in the protocol may be modified during the trial based on newly available PK or PD data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers.

Up to an additional 50 mL sample of blood may be drawn for safety, PK, and/or PD analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Section 12.4).

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK or PD data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (e.g., adding creatinine kinase to serum chemistry panel that was already drawn). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/ERC at the discretion of the investigator.

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 the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

For randomized subjects only, AEs that occur from the time the consent is signed through the time of randomization will only be reported as AEs if they 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. All AEs will be recorded from the time of randomization through 30 days following cessation of treatment (for MK-3475 treated patients), or 14 days following the last blood draw (for non-treated controls), and at each examination, on the AE 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).

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5x the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, 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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial (Last dose of study drug for MK-3475 treated patients, or last blood draw for non-treated controls) or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

Refer to Table 11 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment (for MK-3475 treated patients), or 14 days following the last blood draw (for non-treated controls), or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 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 recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 Surgical complications

All subjects enrolled in this clinical trial will undergo SOC surgical RCC tumor resection. Control subjects will proceed to surgery without study-related treatment, while patients randomized to receive neoadjuvant MK-3475 will proceed to surgery 2-3 weeks following the final MK-3475 dose. As such, any surgical complications in the intra- and postoperative period (30 days from the time of surgery) will be recorded, and will include but will not be limited to the following:

1. the need for and the volume of blood transfusions in the perioperative period
2. hospital readmission following discharge
3. thromboembolic events
4. cardiovascular events
5. pulmonary complications
6. gastrointestinal complications
7. postoperative infection
8. incision-related complications

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 11 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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 test drug	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 there is another obvious cause of the AE. (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.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

Primary Safety

Incidence of adverse experiences will be descriptively summarized for all adverse experiences and Grade 3 or 4 adverse experiences separately. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back- transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary PD Hypothesis

To assess the primary PD hypothesis, the posterior probability that the true response rate is at least 30% will be calculated based on a beta-binomial Bayesian model. A beta prior with parameters α=0.1 and β=0.1 will be assumed. The primary PD hypothesis will be met with at least 80% posterior probability at interim analysis 1, at least 70% posterior probability at interim analysis 2, or at least 60% posterior probability at interim analysis 3.

Interim Analysis: There will be up to 3 interim analyses done for this study. Details of the interim analysis strategy are provided in Section 8.2.6.

Power

Safety

If no AE of a given type is observed in any subject receiving neoadjuvant MK-3475, then the true incidence of the adverse experience at that dose is at most 13%, 10%, 9%, 6%, or 5% with 80% confidence when the sample size among those receiving neoadjuvant MK-3475 is 12, 15, 18, 24 or 33, respectively.

Pharmacodynamics

If the true immune infiltration response rate is 40%, there is ~85% power to meet the primary hypothesis at either the second or third interim analysis, or at the end of the study. If the true response rate is 45%, there is ~85% to meet the primary hypothesis at either the second or third interim analysis. To have high power (>80%) to meet the primary hypothesis after the second interim analysis, the true response rate must be greater than or equal to 55%.

8.2 Statistical Analysis Plan

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Discovery Medicine Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Results Memo for this study.

8.2.1 Hypotheses

Primary (Safety)

Neoadjuvant MK-3475 treatment will be well tolerated in patients undergoing subsequent surgical RCC tumor resection.

Primary (PD)

Neoadjuvant MK-3475 therapy will stimulate a 2-fold or greater increase in intratumoral lymphocytic infiltration in at least 30% of patients with RCC.

Secondary (PD)

1. [redacted]

Tertiary (PD)

8.2.2 Analysis Endpoints

Primary Safety

The primary safety endpoints in this study include all types of adverse experiences, in addition to laboratory safety assessments, ECGs, and vital signs.

Primary PD

The primary PD endpoint in this study is the intratumoral lymphocytic infiltration in patients with RCC. Patients with at least a 2-fold increase in intratumoral lymphocytes will be considered immune cell infiltration responders.

Secondary PD

Tertiary PD

[redacted]

Exploratory PD

There are several exploratory endpoints in this study that include the following:

[redacted]

8.2.3 Approaches to Analyses

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (AST) - All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. Major protocol violators will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the Results Memo for this study. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data

from at least one treatment will be included in the primary analysis dataset. This population will be used for the all PD analyses.

8.2.4 Statistical Methods

Primary Safety

Incidence of adverse experiences will be descriptively summarized for all adverse experiences and Grade 3 or 4 adverse experiences separately. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back- transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

The incidence of intra- and postoperative complications will also be determined. Intra- and postoperative complications are not uncommon in patients undergoing surgical RCC resection, even in those proceeding directly to surgery without any neoadjuvant therapy. In a report of 58 such patients, the transfusion rate was 62.1% (median of 3.5 ± 6.6 units of blood products), and the complication rate was 27.6%, consisting of the need for surgical reexploration (5.2%), hospital readmission (8.6%), thromboembolic complications (1.7%), cardiovascular complications (3.4%), pulmonary complications (6.9%), gastrointestinal complications (10.3%), infectious complications (3.4%) and incision-related complications (6.9%) [79]. The incidence of surgical complications for patients receiving neoadjuvant MK-3475 will be summarized and contrasted with these published complication rates, as the total number subjects in this trial as well as the limited number of untreated controls will be of insufficient power to make accurate within study comparisons.

Primary PD

To assess the primary PD hypothesis, the posterior probability that the true response rate is at least 30% will be calculated based on a beta-binomial Bayesian model. A beta prior with parameters α=0.1 and β=0.1 will be assumed. The primary PD hypothesis will be met with at least 80% posterior probability at interim analysis 1, at least 70% posterior probability at interim analysis 2, or at least 60% posterior probability at interim analysis 3. Additional sensitivity analyses may be performed where the definition of a responder is varied from 2-fold or greater increase in intratumoral lymphocytic infiltration to increases less than 2-fold.

Secondary PD

[redacted]

A two-sample t-test will be used to assess the difference in the expression of pretreatment tumor PD-1 ligands between immune cell infiltration responders and non-responders among patients receiving neoadjuvant MK-3475. If normality is not deemed tenable, data transformations will be considered, or a Wilcoxon rank sum test will be used. If enrollment of controls continues after the first interim analysis, similar analyses may also be done to compare patients receiving MK-3475 relative to controls.

Tertiary PD

[redacted]

[redacted] will be compared using a Bayesian model fit that has a fixed effect for method, and a random effect for patient to account for the within-patient correlation of measurements obtained from the same patient, using flat priors and an assumption of normality. If normality is not tenable, other distributions for the number of TILs may be considered. The posterior probability that the methylation approaches are within +/-10% of the ICH approach will be quantified. A posterior probability of 50% will satisfy this tertiary hypothesis.

Exploratory PD Objectives

Many of the exploratory PD objectives will be addressed using descriptive statistics, including:

- Differences in the IMR expression profiles between RCC tumor antigen-specific CD8+ T cells and unselected TILs in patients that are HLA-A2+
- Stimulation of antigen-specific anti-tumor immune responses in patients with RCC

Other exploratory objectives will be assessed using simple measures of association of potential biomarkers with immune infiltration (i.e., Pearson's or Spearman's correlation):

- Evaluate baseline as well as changes in serum/plasma levels of proteins, miRNAs, exosomes, nucleic acids, circulating antibodies, and other biomarkers after neoadjuvant MK-3475 therapy as potential biomarkers of the immune response to therapy
- Evaluate differences in tumor tissue miRNA expression levels in response to treatment with MK-3475
- Evaluate urine exosomes as a potential biomarker of immunologic response to neoadjuvant MK-3475 treatment
- Assess changes in RCC tumor tryptophan and arginine metabolism in response to MK-3475 treatment

The above objectives may also be assessed using a two-sample t-test to look at differences between immune infiltrate responders and non-responders. If normality is not deemed tenable, data transformations will be considered, or a Wilcoxon rank sum test may be used.

Two-sample t-tests will also be used to identify a possible correlation between clinical response and tumor immune cell infiltration by testing if the magnitude of immune cell infiltration differs between patients who have evidence of a clinical response versus those who do not among patients with metastatic disease. If normality is not deemed tenable, data transformations will be considered, or a Wilcoxon rank sum test may be used.

A paired t-test will be used to assess whether IMR ligand expression changes after treatment with MK-3475 in pre-treatment tumor biopsy tissue and resected tumor. If normality is not deemed tenable, data transformations will be considered, or a Wilcoxon signed rank test will be used.

8.2.5 Multiplicity

Since there is only one primary PD hypothesis, no multiplicity adjustment will be made when testing the primary hypothesis. The secondary and tertiary PD hypotheses will only be tested if the primary PD hypothesis is met. There are six separate secondary hypotheses and more than 8 tertiary hypotheses. Benjamini and Hochberg's false discovery rate multiplicity

adjustment will be applied at a rate of 10% when testing the secondary and tertiary hypotheses.

8.2.6 Interim Analysis

There will be up to 3 interim analyses done for this study. The first interim analysis will be performed after the initial 9 RCC patients, randomized 2:1 to either receive neoadjuvant MK-3475 vs. control (proceed to SOC RCC resection), have all undergone tumor resection and the assessment of tumor immune cell infiltrates has been completed. At the first interim analysis, the number of patients with an immune cell infiltration "response", defined as a 2-fold or greater increase in the immune cell infiltrate in RCC tumor specimens compared with that in the pretreatment tumor biopsy specimens from the same patient, will be examined in the 6 patients receiving neoadjuvant MK-3475. If 4 or more of the first 6 patients receiving neoadjuvant MK-3475 respond, randomization will continue 2:1 to receive either neoadjuvant MK-3475 or control (proceed to SOC RCC resection), respectively, for the remainder of the study. If less than 4 of the first 6 patients receiving neoadjuvant MK-3475 respond, all subsequently enrolled patients may receive neoadjuvant MK-3475 with no further patients being randomized to the control group. Further, if there are 0 or 1 responders in the first 6 patients receiving neoadjuvant MK-3475, then the number of doses of MK-3475 that will be administered in patients subsequently enrolled may be increased from two to three (with the 200 mg dose and the Q3W dosing interval remaining the same). The probabilities of various outcomes after the first interim analysis are provided in Table 12 below, assuming a true immune cell infiltration response rate of 5%, 30%, or 70%.

Table 12 First Interim Analysis Outcome Scenarios

Various outcomes after the first interim analysis assuming a true immune cell infiltration response rate of 5%, 30%, or 70%

Outcome of first interim analysis	Action	Probability if true response rate =		
		5%	30%	70%
0-1 responders	Enroll all subsequent patient to MK-3475, increase from 2 to 3 doses	97%	42%	1%
2-3 responders	Enroll all subsequent patient to MK-3475, continue with 2 doses	3%	51%	24%
4-6 responders	Continue 2:1 randomization (MK-3475:Control)	< 1%	7%	74%

The second interim analysis will occur after a total of 18 RCC patients have undergone tumor resection, with either 15 receiving neoadjuvant MK-3475 with 3 controls or 12 receiving neoadjuvant MK-3475 with 6 controls. The primary PD hypothesis will be assessed, and success will be declared and enrollment may stop if there is at least 80% posterior probability that the true response rate is at least 30%. If success cannot be declared after the initial 18

patients, an additional 9 patients may be enrolled and randomized as determined by the results of the first interim analysis, and a third interim analysis will occur after 27 RCC patients have undergone tumor resection, with either 24 receiving neoadjuvant MK-3475 with 3 controls or 18 receiving neoadjuvant MK-3475 with 9 controls. The primary hypothesis will be assessed, and success will be declared and enrollment may stop if there is at least 70% posterior probability that the true response rate is at least 30%. If success cannot be declared after the initial 27 patients, an additional 9 patients may be enrolled and randomized as determined by the results of the first interim analysis. The final analysis will be performed after 36 RCC patients have undergone tumor resection. At the final analysis, success will be declared if there is at least 60% posterior probability that the true response rate is at least 30%.

After each interim analysis, decisions related to enrolling additional patients may deviate from the rules defined above based on the accumulating data, at the discretion of the Sponsor.

In addition, decisions related to stopping the study for futility may also be considered at each interim analysis. At the second interim analysis, if there are only 0 or 1 responders the study may be stopped for futility. The probability of this happening when the true response rate is 30% is 8.5% (3.5%) with a sample size of 12 (15). At the third interim analysis, if there are 2 or less responders the study may be stopped for futility. The probability of this happening when the true response rate is 30% is 6.0% (1.2%) with a sample size of 18 (24).

8.2.7 Power

Primary Safety: If a serious (Grade 3 or Grade 4) adverse experience occurs at a rate of 1%, 5% or 10% then the chance of observing such an adverse event among the various possible sample sizes are provided in Table 13.

Table 13 Probability of Observing Serious Grade 3 or Grade 4 Adverse Experience for Various AE Rates

Serious AE Rate	Probability (%) of observing serious AE among MK-3475 treated patients				
	$n_{MK} = 12$	$n_{MK} = 15$	$n_{MK} = 18$	$n_{MK} = 24$	$n_{MK} = 33$
1%	11	14	17	21	28
5%	46	54	60	71	82
10%	72	79	85	92	97
n_{MK} = final number of patients receiving neoadjuvant MK-3475					

If no AE of a given type is observed in any subject receiving neoadjuvant MK-3475, then the true incidence of the adverse experience at that dose is at most 13%, 10%, 9%, 6%, or 5% with 80% confidence when the sample size among those receiving neoadjuvant MK-3475 is 12, 15, 18, 24 or 33, respectively.

Primary PD:

Table 14 shows the cumulative probabilities of stopping and declaring success on the primary PD hypothesis after each interim analysis assuming various true immune cell infiltration response rates and implementing the interim analysis strategy as described in Section 8.2.6. If the true immune infiltration response rate is 40%, there is ~85% power to meet the primary hypothesis at either the second or third interim analysis, or at the end of the study. If the true response rate is 45%, there is ~85% to meet the primary hypothesis at either the second or third interim analysis. To have high power (>80%) to meet the primary hypothesis after the second interim analysis, the true response rate must be greater than or equal to 55%.

Table 14 Cumulative Probabilities of Stopping and Declaring Success After Each Interim Analysis Assuming Various True Immune Cell Infiltration Response Rates

True immune cell infiltration response rate	Probability (%) of stopping and declaring success (obtaining stated level of posterior probability that the true immune cell infiltration response rate of MK-3475 at least 30%)		
	After IA 2	After IA 3	At end of study
5%	<0.1	<0.1	<0.1
10%	<0.1	<0.1	0.1
15%	0.3	0.7	1.0
20%	1.7	4.3	6.6
25%	6.3	14.4	22.0
30%	13.0	29.4	44.0
35%	25.5	50.1	67.5
40%	39.2	69.3	84.8
45%	53.6	83.7	94.6
50%	68.7	92.8	98.5
55%	82.0	97.5	99.8
60%	90.1	99.2	>99.9
65%	95.3	99.8	>99.9
70%	98.3	>99.9	>99.9
IA = interim analysis			

If the second interim analysis sample size is 12 (15) receiving neoadjuvant MK-3475, at least 80% posterior probability that the true immune cell infiltration response rate is 30% will be obtained if at least 6 (7) patients respond. If the third interim analysis sample size is 18 (24) receiving neoadjuvant MK-3475, at least 70% posterior probability that the true immune cell infiltration response rate is 30% will be obtained if at least 7 (9) patients respond. If the final analysis sample size is 24 (33) receiving neoadjuvant MK-3475, at least 60% posterior probability that the true immune cell infiltration response rate is 30% will be obtained if at least 6 (11) patients respond. Therefore, the analyses supporting the secondary and tertiary hypotheses will have as few as 6 responders.

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 15.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 15 Product Description

Product Name & Potency	Dosage Form
MK-3475	Lyophilized 50mg/vial

9.2 Packaging and Labeling Information

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

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 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.

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 member 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 or through a secure password-protected electronic portal 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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement.

When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The leftover specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The leftover specimen(s) will be stored to provide a resource for future trials conducted by Merck 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

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, Merck has developed secure policies and procedures. All specimens will be de-identified 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.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

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 Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck 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 Merck 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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 as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. 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.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

13. Questions

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

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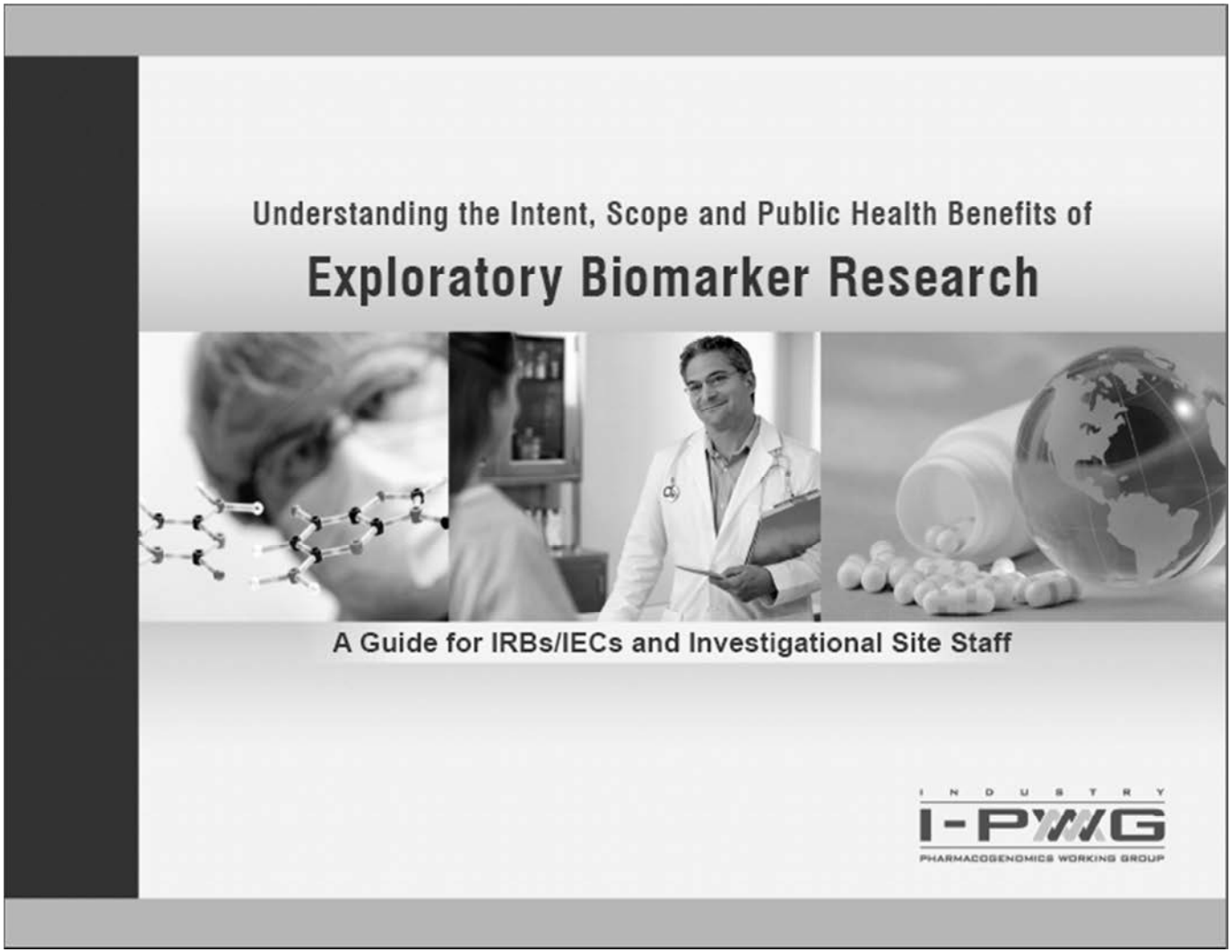
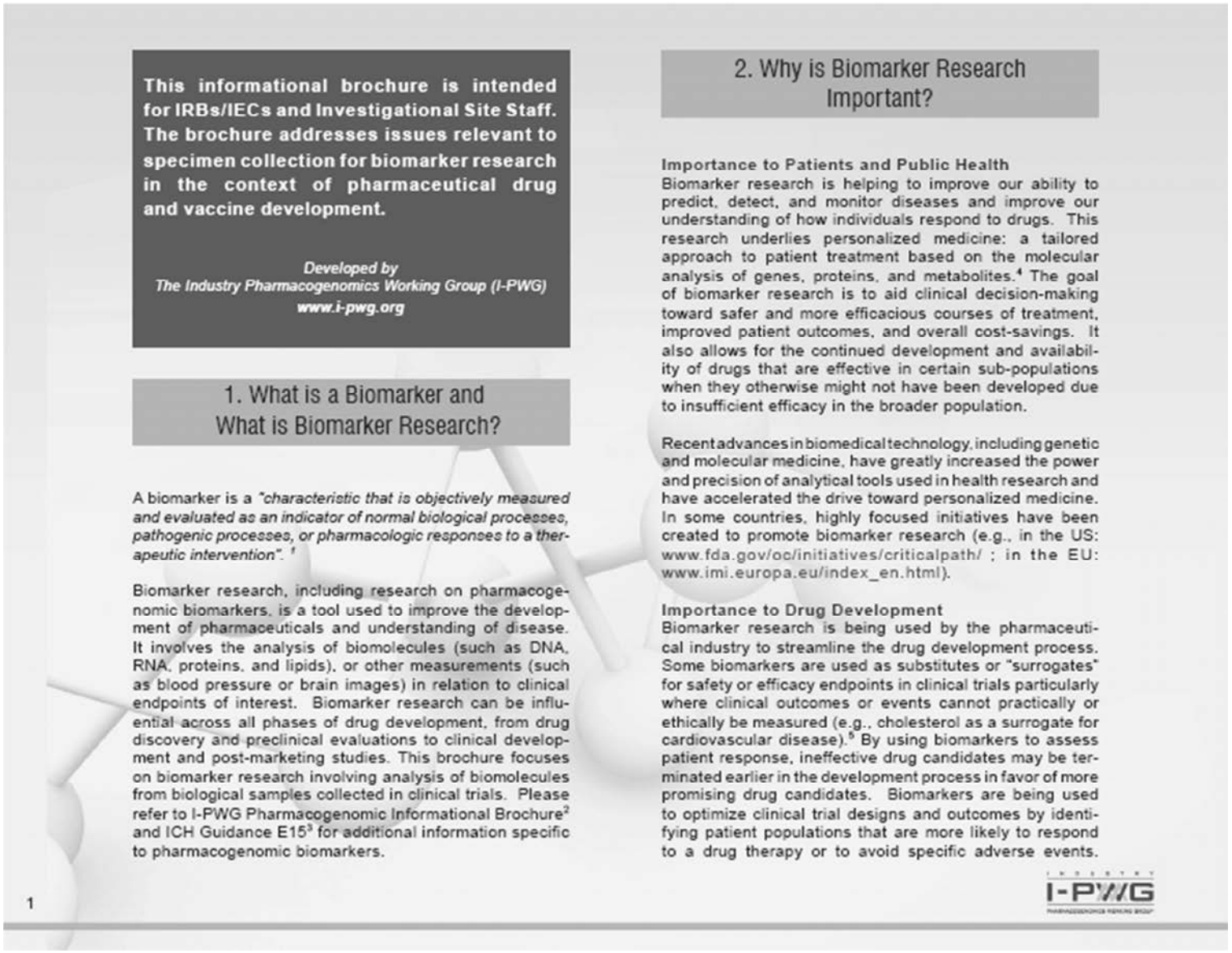
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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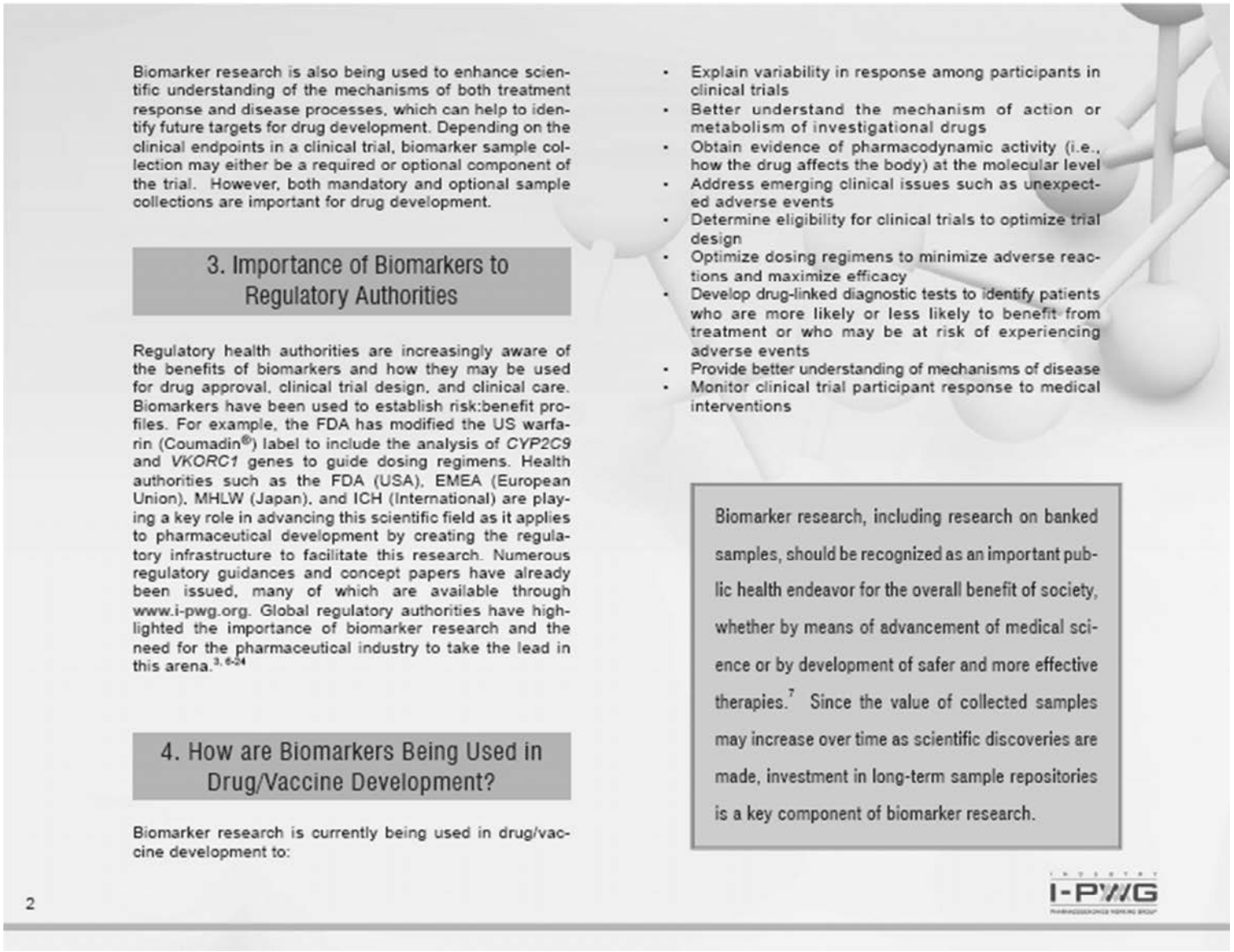
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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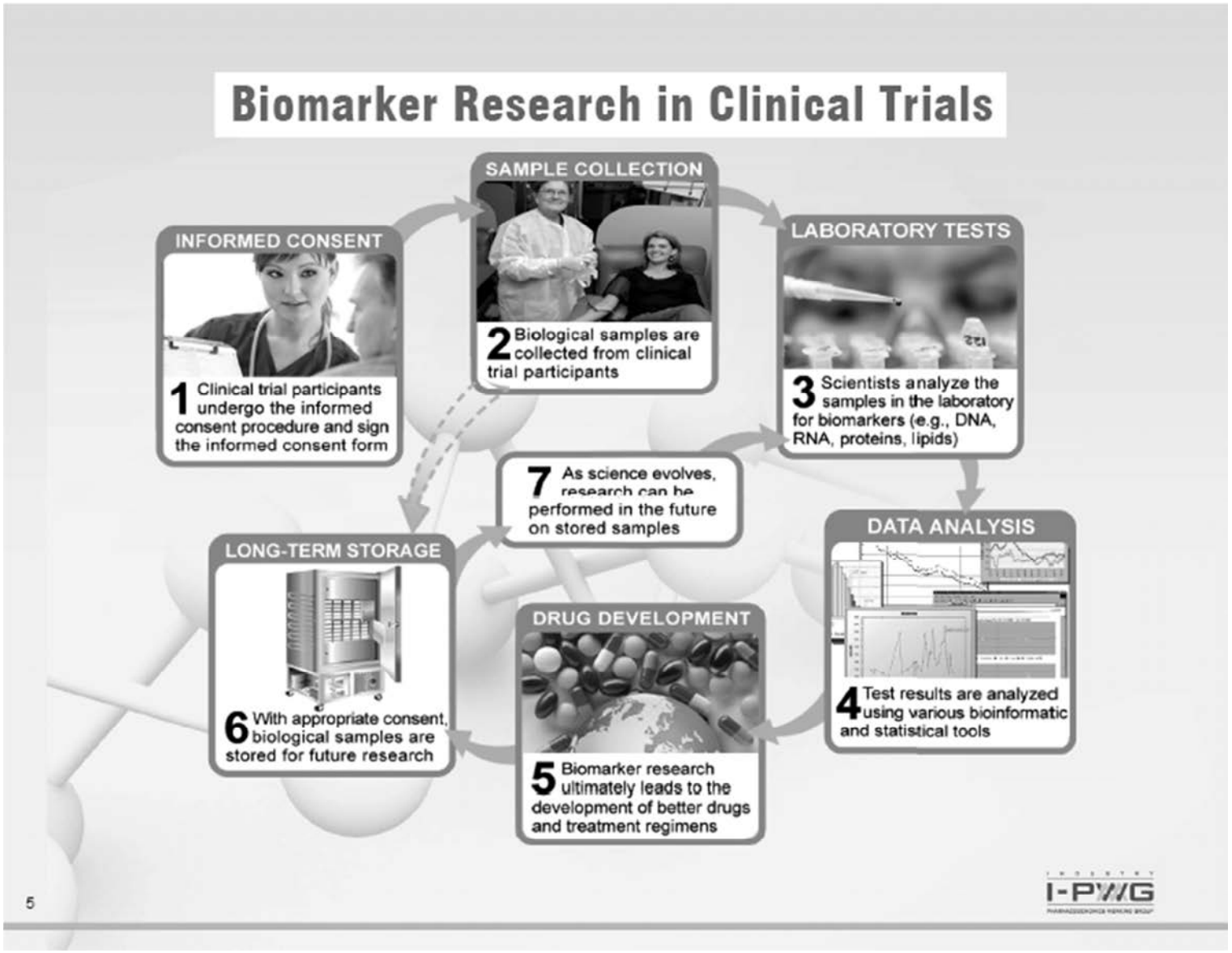
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the 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
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8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

Renegar *et al*. 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.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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

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12.4 Approximate Blood/Tissue/Urine Volumes Drawn/Collected by Trial Visit and by Sample Types

Approximate blood sample volumes that will be collected are listed in Table 16 and Table 17 for patients randomized to receive neoadjuvant MK-3475 or to proceed directly to SOC surgical RCC tumor resection, respectively.

Table 16 Estimated Blood Sample Volumes - Patients Randomized to Neoadjuvant MK-3475

Trial Period:	Screening	Pretreatment Core Biopsy	MK-3475		SOC Tumor Resection	Post-op Follow-up	Post Resection MK-3475
Week:	-2	-1	1	4	7	12	+7[a]
Scheduling window (days)	±14	±6	±3	±3	-7/+14	-5/+7	±7
Thyroid tests and Pregnancy Test-Serum β-HCG/FSH[b] (at screening)	3.5		3.5	3.5	3.5	3.5	
PT/INR and aPTT	3				3		
CBC with Differential	4		4	4	4	4	
Chemistry (includes LFTs)	6		6	6	6	6	
Blood for HLA typing		4					
HIV/Hepatitis Screen (per site SOP)	3.5						
Blood for PBMC Phenotypic Analysis		15			15	15	
Blood for PBMC Isolation and Cryopreservation		64			64	64	64
Blood for plasma collection		20			20	20	
Blood for serum collection (biomarkers)		4			4	4	
Blood for serum collection (PK/PD)			3.5	7	3.5	3.5	
Blood for RNA isolation (PAXgene tube)		2.5			2.5	2.5	
Blood for DNA isolation (PAXgene tube)[c]		8.5			8.5	8.5	
Blood for B cell isolation and transformation						48	
Total Volume of Blood Collected[d]	20	118	17	21.5	134	179	64
Subtotals=	**Neoadjuvant Phase = 488.6**						**64**
							Study Total= 552.6 ml

a. 7 weeks after the first dose of post-resection MK-3475
b. Women of child bearing potential will undergo serum β-HCG testing or women's post-menopausal status will be confirmed by measuring FSH levels.
c. Any leftover DNA may be kept for Future Biomedical Research if the subject signs the FBR consent.
d. If additional pharmacokinetic/pharmacodynamics and/or safety analysis is necessary, additional blood (up to 50 ml) may be obtained. Note: never to exceed 50 ml.

Table 17 Estimated Blood Sample Volumes - Patients Randomized to No Treatment Control Group

Trial Period:	Screening	SOC Tumor Resection	Post-op Follow-up	Post Resection MK-3475
Week	-2	1	6	+7[a]
Scheduling window (days)	±14	±14	-5/+7	±7
Thyroid tests and Pregnancy Test- Serum β-HCG/FSH[b] (at screening)	3.5	3.5	3.5	
PT/INR and aPTT	3	3		
CBC with Differential	4	4	4	
Chemistry (includes LFTs)	6	6	6	
Blood for HLA typing		4		
HIV/Hepatitis Screen (per site SOP)	3.5			
Blood for PBMC Phenotypic Analysis		15	15	
Blood for PBMC Isolation and Cryopreservation		64	64	64
Blood for plasma collection		20	20	
Blood for serum collection		4	4	
Blood for RNA isolation (PAXgene tube)		2.5	2.5	
Blood for DNA isolation (PAXgene tube)[c]		8.5	8.5	
Total Volume of Blood Collected[d]	20	134.5	127.5	64
				Study Total= 346 ml

a. 7 weeks after the first dose of post-resection MK-3475
b. Women of child bearing potential will undergo serum β-HCG testing or women's post-menopausal status will be confirmed by measuring FSH levels.
c. Any leftover DNA may be kept for Future Biomedical Research if the subject signs the FBR consent.
d. If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 ml) may be obtained. Note: never to exceed 50 ml.

Approximate tissue sample volumes (tumor and adjacent non-malignant kidney tissue) that will be collected are listed in Table 18 and Table 19 for patients randomized to receive neoadjuvant MK-3475 or to proceed directly to SOC surgical RCC tumor resection, respectively.

Table 18 Estimated Tissue Sample Volumes - Patients Randomized to Neoadjuvant MK-3475

Trial Period:	**Pretreatment Core Biopsy**	**MK-3475**		**SOC Tumor Resection**
Week:	-1	1	4	7
Scheduling window (days)	±6	±3	±3	-7/+14
Tumor Core Needle Biopsy- Pretreatment	Approximately 0.06 cm^3			
Fresh tumor tissue for shipping (TIL analysis, histoculture, tumor cell isolation and IMR expression analysis)				10 cm^3
Intraoperative Tumor Core Needle Biopsy				Approximately 0.06 cm^3
Tumor tissue for FFPE (IHC; DNA for mutational analysis, TCR utilization, promoter methylation analysis; RNA for gene expression and miRNA analysis)				Three pieces, each 0.5 cm x 0.5 cm x 0.3 cm Total Volume = 0.225 cm^3
Fresh tumor tissue for storage in RNA later solution (RNA extraction-gene expression, miRNA analysis)				One piece, 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.125 cm^3
Fresh tumor tissue for snap freezing (DNA isolation, metabolic profiling, laser capture microdissection)				Three pieces, each 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.375 cm^3
Fresh non-malignant kidney tissue from resected tumor specimen for snap freezing (DNA isolation)				One piece, 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.125 cm^3
Fresh non-malignant kidney tissue in RNAlater solution (RNA extraction, gene expression)				One piece, 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.125 cm^3
Volumes =	0.06 cm^3			10.98 cm^3
Approximate Total Volume of Tissue Samples =				**11.0 cm^3**

Table 19 Estimated Tissue Sample Volumes - Patients Randomized to No Treatment Control Group

Trial Period:	Screening	SOC Tumor Resection
Week	-2	-2
Scheduling window (days)	±14	±14
Fresh tumor tissue for shipping (TIL analysis, histoculture, tumor cell isolation and IMR expression analysis)		10 cm^3
Intraoperative Tumor Core Needle Biopsy		Approximately 0.06 cm^3
Tumor tissue for FFPE (IHC; DNA for mutational analysis, TCR utilization, promoter methylation analysis; RNA for gene expression and miRNA analysis)		Three pieces, each 0.5 cm x 0.5 cm x 0.3 cm Total Volume = 0.225 cm^3
Fresh tumor tissue for storage in RNA later solution (RNA extraction-gene expression, miRNA analysis)		One piece, 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.125 cm^3
Fresh tumor tissue for snap freezing (DNA isolation, metabolic profiling, laser capture microdissection)		Three pieces, each 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.375 cm^3
Fresh non-malignant kidney tissue from resected tumor specimen for snap freezing (DNA isolation)		One piece, 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.125 cm^3
Fresh non-malignant kidney tissue in RNAlater solution (RNA extraction, gene expression)		One piece, 0.5 cm x 0.5 cm x 0.5 cm Total Volume = 0.125 cm^3
Approximate Total Volume of Tissue Samples =		**11.0 cm^3**

Approximate urine volumes that will be collected for research analysis are listed in Table 20 and Table 21 for patients randomized to receive neoadjuvant MK-3475 or to proceed directly to SOC surgical RCC tumor resection, respectively.

Table 20 Estimated Urine Sample Volumes - Patients Randomized to Patients Randomized to Neoadjuvant MK-3475

Trial Period:	Pretreatment Core Biopsy	SOC Tumor Resection	Follow-up
Week:	-1	7	12
Scheduling window (days)	±6	-7/+14	-5/+7
Urine for exosome isolation and analysis	100 ml	100 ml	100 ml
Total volume of urine collected=	300 ml		

Table 21 Estimated Urine Sample Volumes – Patients Randomized to No Treatment Control Group

Trial Period:	**SOC Tumor Resection**	**Follow-up**
Week:	2	6
Scheduling window (days)	±14	-5/+7
Urine for exosome isolation and analysis	100 ml	100 ml
Total volume of urine collected=	200 ml	

12.5 List of Abbreviations and Definitions

Abbreviation/Term	Definition
AE	Adverse Event
ASCO	American Society of Clinical Oncology
AST	All Subjects as Treated
ARG1	Arginase 1
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	formalin-fixed paraffin-embedded
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
IHC	immunohistochemical
IDO	indoleamine 2,3-dioxygenase
IMR	immune modulatory receptor
iNOS	inducible nitric oxide synthase
irAEs	Immune-Related Adverse Events
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
LAG-3	lymphocyte activation gene 3
MEL	Melanoma
MDSC	myeloid derived suppressor cell
NCI	National Cancer Institute
NCS	not clinically significant
NHANES	National Health and Nutrition Examination Survey
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
PGT	Pharmocogenetic
PD	Pharmacodynamic
PD-1	programmed cell death-1
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PP	Per-Protocol
Q2W	every 2 weeks
Q3W	every 3 weeks

Abbreviation/Term	Definition
RCC	renal cell cancer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	standard of care
SOP	standard operating procedure
TCR	T cell receptor
Tigit	T cell immunoreceptor with Ig and ITIM domains
TILs	tumor infiltrating lymphocytes
V-type	Variable-type

12.6 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting (http://ctep.cancer.gov/reporting/ctc.html).

12.7 Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead
*As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.8 Algorithm for Assessing Out-of-Range Laboratory Values

For all laboratory values obtained at pre-study (screening) visit and/or pre-dose evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The subject may be excluded from the study.

   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. The subject may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (*e.g.,* elevated eosinophil count in a subject with asthma or seasonal allergies) the medical condition should be annotated on the laboratory report or

   4. The abnormal test may be repeated (refer to items a. and b. below for continuation of algorithm for repeated values). Unless a spurious result is suspected, repeat testing for any given abnormal laboratory screening test result will only be performed once.

      a. If the repeat test value is within the normal range, the subject may enter the study.

      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the subject will be excluded from the study.

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 – 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	