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TITLE:

A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer

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TABLE OF CONTENTS

SUMMARY OF CHANGES	10
1.0 TRIAL SUMMARY	12
2.0 TRIAL DESIGN	13
2.1 Trial Design	13
2.2 Trial Diagram	15
3.0 OBJECTIVE(S) & HYPOTHESIS(ES)	16
3.1 Primary Objective(s) & Hypothesis(es)	16
3.2 Secondary Objective(s) & Hypothesis(es)	16
3.3 Exploratory Objective(s) & Hypothesis(es)	17
4.0 BACKGROUND & RATIONALE	17
4.1 Background	17
4.1.1 Pharmaceutical and Therapeutic Background	17
4.1.2 Pre-clinical and Clinical Trials	18
4.1.3 Ongoing Clinical Trials.....	19
4.2 Rationale	19
4.2.1 Rationale for the Trial and Selected Subject Population	19
4.2.2 Rationale for Dose Selection/Regimen/Modification	21
4.2.3 Rationale for Endpoints	22
4.2.3.1 Efficacy Endpoints.....	22
4.2.3.1.1 Primary.....	22
4.2.3.1.2 Secondary.....	23
4.2.3.1.3 Exploratory	23
4.2.3.1.3.1 Patient Reported Outcomes	23
4.2.3.2 Safety Endpoints	24
4.2.3.3 Planned Exploratory Biomarker Research.....	24
4.2.3.4 Future Biomedical Research	26
4.3 Benefit/Risk	27
5.0 METHODOLOGY	27
5.1 Entry Criteria	27
5.1.1 Diagnosis/Condition for Entry into the Trial	27

5.1.2	Subject Inclusion Criteria.....	27
5.1.3	Subject Exclusion Criteria	30
5.2	Trial Treatment(s)	32
5.2.1	Dose Selection/Modification	32
5.2.1.1	Dose Selection (Preparation)	32
5.2.1.2	Dose Modification and Toxicity Management Guidelines	32
5.2.2	Timing of Dose Administration	37
5.2.2.1	Pembrolizumab (MK-3475).....	37
5.2.3	Trial Blinding/Masking.....	38
5.3	Randomization or Treatment Allocation.....	38
5.4	Stratification.....	38
5.5	Concomitant Medications/Vaccinations (Allowed & Prohibited).....	38
5.5.1	Acceptable Concomitant Medications	38
5.5.2	Prohibited Concomitant Medications.....	39
5.6	Rescue Medications & Supportive Care	40
5.6.1	Supportive Care Guidelines	40
5.7	Diet/Activity/Other Considerations.....	40
5.7.1	Diet.....	40
5.7.2	Contraception.....	40
5.7.3	Use in Pregnancy	41
5.7.4	Use in Nursing Women.....	41
5.8	Subject Withdrawal/Discontinuation Criteria.....	41
5.8.1	Treatment after initial evidence of radiologic disease progression.....	43
5.8.2	Discontinuation of Study Therapy after CR	44
5.9	Subject Replacement Strategy	45
5.10	Beginning and End of the Trial	45
5.11	Clinical Criteria for Early Trial Termination	45
6.0	TRIAL FLOW CHART	46
6.1	Initial Treatment Phase.....	46
6.2	Second Course Phase (Retreatment).....	50
7.0	TRIAL PROCEDURES	52
7.1	Trial Procedures	52

7.1.1	Administrative Procedures	52
7.1.1.1	Informed Consent	52
7.1.1.1.1	General Informed Consent	52
7.1.1.1.2	Consent and Collection of Specimens for Future Biomedical Research	53
7.1.1.2	Inclusion/Exclusion Criteria	53
7.1.1.3	Subject Identification Card	53
7.1.1.4	Medical History	53
7.1.1.4.1	Disease Details	53
7.1.1.5	Prior and Concomitant Medications Review	53
7.1.1.5.1	Prior Medications	53
7.1.1.5.1.1	Prior Treatment Details for Urothelial Cancer	54
7.1.1.5.2	Concomitant Medications	54
7.1.1.5.2.1	Subsequent Anti-Cancer Therapy Status	54
7.1.1.6	Assignment of Screening Number	54
7.1.1.7	Assignment of Randomization Number	54
7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	55
7.1.2	Clinical Procedures/Assessments	55
7.1.2.1	Adverse Event (AE) Monitoring	55
7.1.2.2	Physical Exam	55
7.1.2.2.1	Full Physical Exam	55
7.1.2.2.2	Directed Physical Exam	56
7.1.2.3	Vital Signs	56
7.1.2.4	12-Lead Electrocardiogram (ECG)	56
7.1.2.5	Eastern Cooperative Oncology Group (ECOG) Performance Status	56
7.1.2.6	Tumor Imaging and Assessment of Disease	56
7.1.2.6.1	Initial Tumor Imaging	57
7.1.2.6.2	Tumor Imaging During Trial	57
7.1.2.6.3	Bone Scans	57
7.1.2.6.4	Assessment of Disease	58
7.1.2.7	Tumor Tissue Collection and Correlative Blood Sampling	58
7.1.2.8	Patient Reported Outcomes (PROs)	59

7.1.3	Laboratory Procedures/Assessments	59
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) ..	60
7.1.3.2	Pharmacokinetic/Pharmacodynamic Evaluations	61
7.1.3.3	Future Biomedical Research	61
7.1.4	Other Procedures	61
7.1.4.1	Withdrawal/Discontinuation	61
7.1.4.1.1	Withdrawal From Future Biomedical Research	61
7.1.4.2	Blinding/Unblinding	62
7.1.4.3	Calibration of Critical Equipment.....	62
7.1.5	Visit Requirements.....	62
7.1.5.1	Screening.....	62
7.1.5.2	Treatment Period/Vaccination Visit	63
7.1.5.2.1	Second Course Phase (Retreatment Period)	63
7.1.5.3	Post-Trial.....	65
7.1.5.3.1	Safety Follow-up Visit.....	65
7.1.5.3.2	Follow-up Visits	65
7.1.5.3.3	Survival Follow-up	65
7.1.5.4	Survival Status	66
7.2	Assessing and Recording Adverse Events	66
7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor.....	67
7.2.2	Reporting of Pregnancy and Lactation to the Sponsor	67
7.2.3	Immediate Reporting of Adverse Events to the Sponsor	68
7.2.3.1	Serious Adverse Events	68
7.2.3.2	Events of Clinical Interest.....	69
7.2.3.3	Protocol-Specific Exceptions to Serious Adverse Event Reporting	70
7.2.4	Evaluating Adverse Events	70
7.2.5	Sponsor Responsibility for Reporting Adverse Events	73
7.3	Trial Governance and Oversight.....	73
7.3.1	Scientific Advisory Committee.....	73
8.0	STATISTICAL ANALYSIS PLAN	73
8.1	Statistical Analysis Plan Summary	73

8.1.1	Efficacy Analyses	74
8.1.2	Safety Analyses.....	74
8.1.3	Power and Sample Size.....	74
8.1.4	Biomarker/Interim Analysis.....	74
8.2	Statistical Analysis Plan	74
8.2.1	Responsibility for Analyses/In-House Blinding.....	74
8.2.2	Hypotheses/Estimation	75
8.2.3	Analysis Endpoints	75
8.2.3.1	Efficacy Endpoints.....	75
8.2.3.2	Safety Endpoints	75
8.2.4	Analysis Populations.....	75
8.2.4.1	Efficacy Analysis Population.....	75
8.2.4.2	Safety Analysis Population	76
8.2.4.3	Biomarker Discovery Population.....	76
8.2.5	Statistical Methods.....	76
8.2.5.1	Statistical Methods for Efficacy Analyses	76
8.2.5.2	Statistical Methods for Safety Analyses	77
8.2.5.3	Statistical Methods for Biomarker Analyses	77
8.2.5.4	Summaries of Baseline Characteristics, Demographics, and Other Analyses.....	78
8.2.5.4.1	Demographic and Baseline Characteristics	78
8.2.6	Multiplicity	78
8.2.7	Sample Size and Power Calculation	78
8.2.8	Subgroup Analyses and Effect of Baseline Factors	80
8.2.9	Interim Analyses	80
8.2.10	Compliance (Medication Adherence).....	80
8.2.11	Extent of Exposure.....	81
9.0	LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES	81
9.1	Investigational Product	81
9.2	Packaging and Labeling Information	81
9.3	Clinical Supplies Disclosure.....	81

9.4	Storage and Handling Requirements	81
9.5	Discard/Destruction/Returns and Reconciliation	82
9.6	Standard Policies.....	82
10.0	ADMINISTRATIVE AND REGULATORY DETAILS.....	82
10.1	Confidentiality.....	82
10.1.1	Confidentiality of Data	82
10.1.2	Confidentiality of Subject Records	82
10.1.3	Confidentiality of Investigator Information	83
10.1.4	Confidentiality of IRB/IEC Information.....	83
10.2	Compliance with Financial Disclosure Requirements.....	83
10.3	Compliance with Law, Audit and Debarment	84
10.4	Compliance with Trial Registration and Results Posting Requirements	86
10.5	Quality Management System.....	86
10.6	Data Management.....	86
10.7	Publications	86
11.0	LIST OF REFERENCES.....	88
12.0	APPENDICES.....	93
12.1	Merck Code of Conduct for Clinical Trials.....	93
12.2	Collection and Management of Specimens for Future Biomedical Research.....	95
12.3	Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff	101
12.4	Abbreviations	112
12.5	ECOG Performance Status.....	115
12.6	New York Heart Association (NYHA) Functional Classification	116
12.7	Common Terminology Criteria for Adverse Events V4.0 (CTCAE).....	117
12.8	Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria For Evaluating Response in Solid Tumors	118
13.0	SIGNATURES.....	119
13.1	Sponsor's Representative	119
13.2	Investigator	119

LIST OF TABLES

Table 1	Adequate Organ Function Laboratory Values	29
Table 2	Trial Treatment	32
Table 3	Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.....	33
Table 4	Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines	36
Table 5	Imaging and Treatment After 1st Radiologic Evidence of PD	44
Table 6	Laboratory Tests	60
Table 7	Evaluating Adverse Events	71
Table 8	Analysis Strategy for Efficacy Endpoints.....	78
Table 9	Estimates and 95% CIs with 60 PD-L1 Strongly Positive Subjects	79
Table 10	Estimates and 95% CIs with 75 PD-L1 Strongly Positive Subjects	79
Table 11	Product Descriptions	81

LIST OF FIGURES

Figure 1	Trial Design	15
Figure 2	Best Percent Change from Baseline in Target Lesions by Best Objective Response (Full Analysis Set Population, by Investigator Assessment) KEYNOTE-012	20

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2 5.6.1 Table 3 Table 4	Dose Modification and Toxicity Management Guidelines for Pembrolizumab Supportive Care Guidelines Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines	Added guidelines for dose modification in the event of myocarditis and updated guidelines for several other conditions. Also reorganized content into new tables and under new section headings.	To align with the most current label and safety information for pembrolizumab.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0 7.1.5.3.3 7.1.5.4	Trial Flow Chart Survival Follow-up Survival Status	Added flexibility to perform survival follow-up as requested by the Sponsor, in addition to the regularly scheduled assessments.	To allow the Sponsor to collect information as needed to support ongoing analyses of the study survival data.
4.2.2 6.0 7.1.3.2	Rationale for Dose Selection/Regimen/Modification Trial Flow Chart Pharmacokinetic/Pharmacodynamic Evaluations	Updated the rationale for the 200 mg Q3W dose of pembrolizumab. Removed the collection of PK and ADA samples.	200 mg Q3W is now the approved, standard dose for pembrolizumab across indications.

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase II Trial of Pembrolizumab (MK-3475) in Subjects with Bladder Cancer
Trial Phase	II
Clinical Indication	1L Cisplatin-ineligible Advanced/Unresectable or Metastatic Urothelial Cancer
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
(Select Groups)	pembrolizumab (MK-3475) 200 mg every 3 weeks
Number of trial subjects	Approximately up to 350 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	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 28 days, each eligible subject will receive treatment with pembrolizumab (MK-3475) on Day 1 of each 3 week cycle. Treatment with pembrolizumab (MK-3475) will continue until disease progression is confirmed by the investigator/site radiologist, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 24 months of trial treatment, or administrative reasons. Subjects receiving pembrolizumab (MK-3475) who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects who stop trial treatment after receiving 24 months of trial treatment for reasons other than disease progression or intolerability, or subjects who attain a complete response and stop trial treatment may be eligible for up to one year of retreatment upon experiencing disease progression. The decision to retreat will be at the discretion of the investigator only if the subject meets the criteria for retreatment after experiencing disease progression and the trial is ongoing. After the end of treatment each subject will be followed for 30 days for adverse event monitoring or before the initiation of new anti-cancer therapy, whichever comes first. Serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status every 6 weeks (\pm 7 days) in the first year and every 12 weeks (\pm 7 days) after year 1 until disease progression is confirmed by the investigator/site radiologist, a non-study cancer treatment is initiated, consent is withdrawn, until death, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival every 12 weeks (\pm 7 days) until death, withdrawal of consent, or the end of the trial.

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-site, open-label trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer, who have not received prior systemic chemotherapy (i.e., first line, 1L) and who are not eligible to receive cisplatin, to be conducted in conformance with Good Clinical Practices.

Approximately up to 350 subjects may be enrolled and will provide newly obtained formalin fixed paraffin embedded (FFPE) tumor biopsies for PD-L1 determination by immunohistochemistry (IHC). PD-L1 positive/negative population is defined as subjects with PD-L1 IHC assay result (Combined Positive Score - CPS) higher/lower than the PD-L1 cut-point 1%.

Samples for PD-L1 determination will be sent to a central laboratory for real time evaluation to ensure adequate tissue specimen is present. Additionally, all subjects must have confirmed measurable disease based on RECIST 1.1 as determined by central radiology review. All subjects will receive pembrolizumab (MK-3475) regardless of PD-L1 status. Subjects will be administered pembrolizumab (MK-3475) 200 mg every three weeks (Q3W). Neoadjuvant/Adjuvant platinum based chemotherapy, with recurrence >12 months from completion of therapy, is permitted.

Subjects will be evaluated at 9 weeks (\pm 7 days) after the first dose of trial treatment on Day 1 Cycle 1, and every 6 weeks (\pm 7 days) thereafter with radiographic imaging to assess response to treatment. Subjects who remain on treatment beyond a year will have imaging performed every 12 weeks (\pm 7 days) thereafter. All imaging obtained on study will be submitted for an independent radiologist's review, who will assess the images using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS). The investigator may choose to treat beyond RECIST 1.1 defined progression in subjects considered to be deriving clinical benefit and who are clinically stable.

Adverse events will 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 pembrolizumab (MK-3475) will continue until documented disease progression by investigator/site radiologist, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab (MK-3475), or administrative reasons.

Subjects who attain an investigator-determined confirmed complete response (CR), may consider stopping trial treatment after receiving at least 24 weeks of treatment. Subjects who discontinue for reasons other than disease progression or intolerability, or who discontinue after attaining a CR may be eligible for up to one year of retreatment after they have

experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab (MK-3475), the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.2.1 for further details).

After the end of treatment each subject will be followed for 30 days (\pm 3 days) for adverse event monitoring or before the initiation of new anti-cancer therapy, whichever comes first. Serious adverse events and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status every 6 weeks (\pm 7 days) in the first year and every 12 weeks (\pm 7 days) after year 1 until disease progression is confirmed by the investigator/site radiologist, a non-study cancer treatment is initiated, consent is withdrawn, until death, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival every 12 weeks (\pm 7 days) until death, withdrawal of consent, or the end of the trial.

The primary objective of this study is to evaluate the anti-tumor activity of pembrolizumab (MK-3475) as first line (1L) therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy and whose tumors express PD-L1 protein by IHC based on ORR (RECIST 1.1) assessed by independent radiology review. Data from previously conducted pembrolizumab bladder cancer trials will be utilized to determine a biomarker assay cut-point. In the event a cut-point cannot be determined from data from previous studies, additional subjects will be added to the beginning of this study to supplement the previously collected data in order to determine the assay cut-point. In this case, data from subjects in the main part of the trial to assess the primary endpoint will be kept separate, and will be analyzed separately once the cut-point has been determined.

The all-patient-treated (APT) population will serve as the primary population for the analyses of efficacy data in this trial. Supportive analyses of efficacy will be conducted in the full analysis set (FAS) population as well. The APT population consists of all treated subjects. The FAS population consists of all enrolled subjects who receive at least one dose of study treatment and have measurable disease at baseline. Interim futility analysis with PD-L1 negative subjects is planned and enrollment of PD-L1 negative subjects may be stopped after the interim analysis.

Participation in this trial will be dependent upon supplying tumor tissue obtained at any time before the first dose of study drug, as long as the subject has not received any intervening systemic therapy from the time the tissue was collected until the time the subject enters the study.

Additionally, tumor tissue must be obtained from locations not radiated prior to biopsy; newly obtained formalin-fixed specimens AFTER the subject has been diagnosed with

metastatic or muscle invasive disease will be required for determination of PD-L1 status. Biopsies obtained PRIOR to receipt of neoadjuvant/adjuvant chemotherapy are NOT permitted. Subjects who received neoadjuvant/adjuvant therapy are permitted onto the trial as long as therapy was completed at least 12 months prior to the diagnosis of metastatic disease.

Only tumor specimens obtained AFTER completion of the neoadjuvant/adjuvant therapies and only AFTER metastatic or muscle invasive disease is observed will be used to assess PD-L1 status. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a retrospective manner, thus tissue availability, but not high biomarker expression is required for trial entry.

Additionally, if available, archived tumor tissue specimens from prior biopsies will be collected for determination of PD-L1 status to compare biomarker expression in archived specimens against the in newly obtained tumor tissue that is collected as a requirement for entry into the trial.

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

2.2 Trial Diagram

The trial design is depicted in [Figure 1](#).

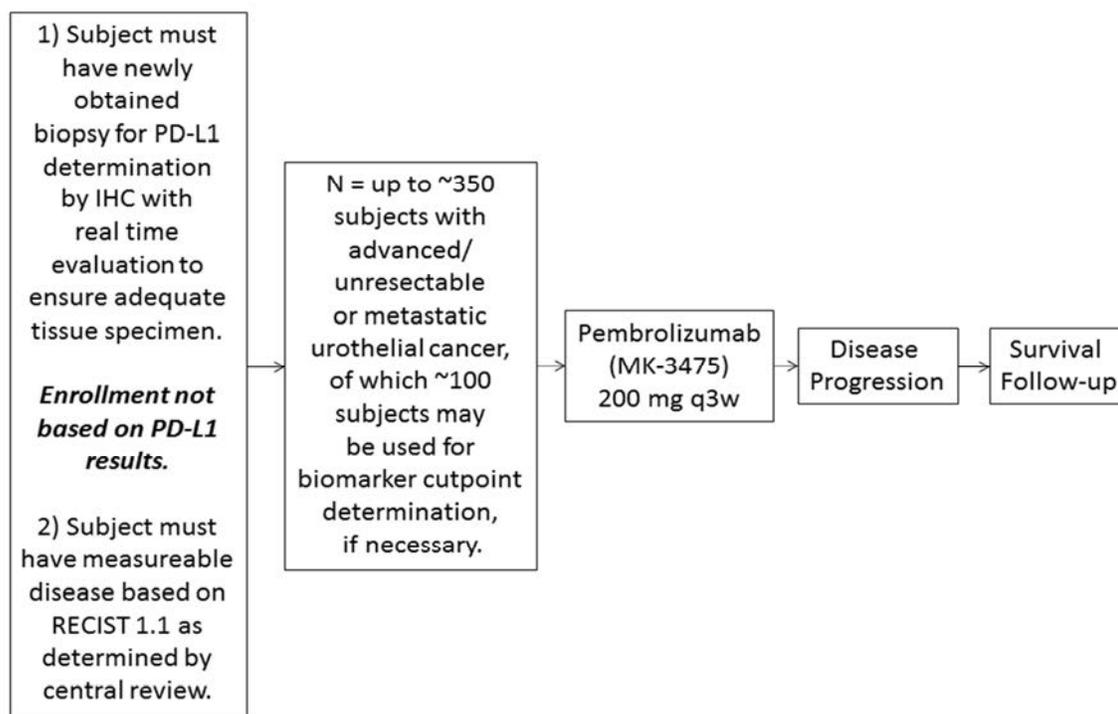


Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subject with advanced/unresectable or metastatic urothelial cancer who are ineligible to receive cisplatin-based therapy, evaluate anti-tumor activity of pembrolizumab (MK-3475) as 1L therapy:

1. Objective: By objective response rate (ORR) based on RECIST 1.1 by independent radiology review in all subjects.
2. Objective: By ORR based on RECIST 1.1 by independent radiology review in subjects whose tumors are PD-L1 positive (Combined Positive Score or CPS \geq 1%).
3. Objective: By ORR based on RECIST 1.1 by independent radiology review in subjects whose tumors are PD-L1 strongly positive (CPS cut-point determined from biomarker discovery population; see Section 8.2).

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with advanced/unresectable or metastatic urothelial cancer who are ineligible to receive cisplatin-based therapy:

1. Objective: To evaluate the anti-tumor activity of pembrolizumab (MK-3475) as 1L therapy in PD-L1 strongly positive, PD-L1 positive and all subjects
 - By duration of response (DOR) based on RECIST 1.1 by independent radiology review.
 - By progression-free survival (PFS) based on RECIST 1.1 by independent radiology review and overall survival (OS).
 - By PFS rate based on RECICST 1.1 by independent radiology review and OS rate at 6 and 12 months.
2. Objective: To establish a cut-point for PD-L1 strongly positive status if this is not determined by other biomarker discovery populations, investigate the association between PD-L1 protein expression by IHC and anti-tumor activity.
3. Objective: To determine the safety and tolerability of pembrolizumab (MK-3475) as 1L therapy.

3.3 Exploratory Objective(s) & Hypothesis(es)

In subjects with advanced/unresectable or metastatic urothelial cancer who are ineligible to receive cisplatin-based therapy:

1. Objective: To investigate the relationship between candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab (MK-3475) utilizing pre- and post-treatment tumor biopsies and blood sampling in PD-L1 strongly positive, PD-L1 positive and all subjects, respectively.
2. Objective: To explore the PK profile of pembrolizumab (MK-3475) 200 mg Q3W as 1L therapy in PD-L1 strongly positive, PD-L1 positive and all subjects, respectively.
3. Objective: To evaluate changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30, in PD-L1 strongly positive, PD-L1 positive and all subjects, respectively.
4. Objective: To characterize utilities using the EuroQol EQ-5D, in PD-L1 strongly positive, PD-L1 positive and all subjects, respectively.
5. Objective: To Evaluate anti-tumor activity of pembrolizumab (MK-3475) as 1L therapy in PD-L1 strong positive, PD-L1 positive and all subjects by ORR, DOR and PFS based on modified RECIST 1.1 by independent radiology review.

Note: If a strongly positive cut-off with clinical utility beyond 1% cannot be identified from the biomarker analysis, the objectives with strongly positive subjects will not be pursued.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (previously known as MK-3475 and SCH 9000475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. 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 many solid tumors.

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 of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. 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 CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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 [18; 19; 20; 13]. 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 [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. 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.

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 mono-therapy 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 [22; 23; 24; 25; 26; 27]. 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 melanoma, non-small cell lung cancer, a number of advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure.

An open-label Phase I trial (KEYNOTE-012) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475) in advanced solid tumors including triple negative breast cancer, head and neck cancer, urothelial cancer and gastric cancer. Subjects with advanced urothelial cancer who express PD-L1 in the tumor and surrounding microenvironment were enrolled into an initial cohort and treated with pembrolizumab (MK-3475) at 10 mg/kg every 2 weeks. Promising preliminary anti-cancer activity has been observed in these subjects. These data show a best objective response of 25% (7 of 28 subjects in the full analysis set). Thirty-three (33) subjects were included in the safety analysis of the urothelial cohort and of these subjects, 97% experienced ≥ 1 AE, and 58% reported a drug-related AE. At least one Grade 3-5 AE was reported in 57% of subjects, with 12% reporting a drug-related Grade 3-5 AE.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Urothelial (transitional cell) cancer describes a range of tumors that arise from the urothelial endothelium, which includes the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually, ranking it as the seventh most common cancer worldwide [28]. Urothelial carcinoma is the predominant histologic type of bladder cancer in the United States and Western Europe, where it accounts for approximately 90 percent of bladder cancers. In other areas of the world, nonurothelial histologies are more frequent.

Cisplatin-based combination chemotherapy is standard first-line treatment for patients with advanced bladder cancer based on randomized trials [29; 30; 31; 32; 33; 34]. The median survival with these regimens is 13 to 15 months, and 5% to 15% of patients attain long-term survival. However, cisplatin ineligibility is common because of renal dysfunction (creatinine clearance < 60 mL/min) or performance status of 2, or both. Furthermore, hearing loss, Grade 2 neuropathy, heart failure, and age-associated diminished renal function may also confer cisplatin ineligibility [35; 36; 37].

Carboplatin is often substituted for cisplatin in such patients, but it is associated with inferior outcomes, as demonstrated in a meta-analysis of randomized Phase II trials [36; 38]. A Phase III trial comparing gemcitabine/carboplatin (GC) with MCAVI (methotrexate/carboplatin/vinblastine) in cisplatin-ineligible patients demonstrated a median survival of

only 8 to 9 months with both regimens [39]. Notably, those with both poor renal function and poor performance status fared especially poorly with combination chemotherapy in this trial. Thus, there remains a significant unmet medical need for well-tolerated active therapies in this population. According to the National Comprehensive Cancer Network guidelines, clinical trials of potentially less toxic therapies are recommended for this population of patients.

This study administers pembrolizumab (MK-3475) as 1st line therapy. Based on the known toxicity profile of pembrolizumab (MK-3475), it is unlikely that initial treatment with pembrolizumab will preclude subsequent treatment with gemcitabine/carboplatin, or other regimens, for those patients who desire such treatment. Results from KEYNOTE-012 demonstrate that nearly half of pembrolizumab treated patients experienced tumor shrinkage with very limited toxicity, and suggest that an initial trial with pembrolizumab may be reasonable and worthwhile for cisplatin ineligible patients (Figure 2).

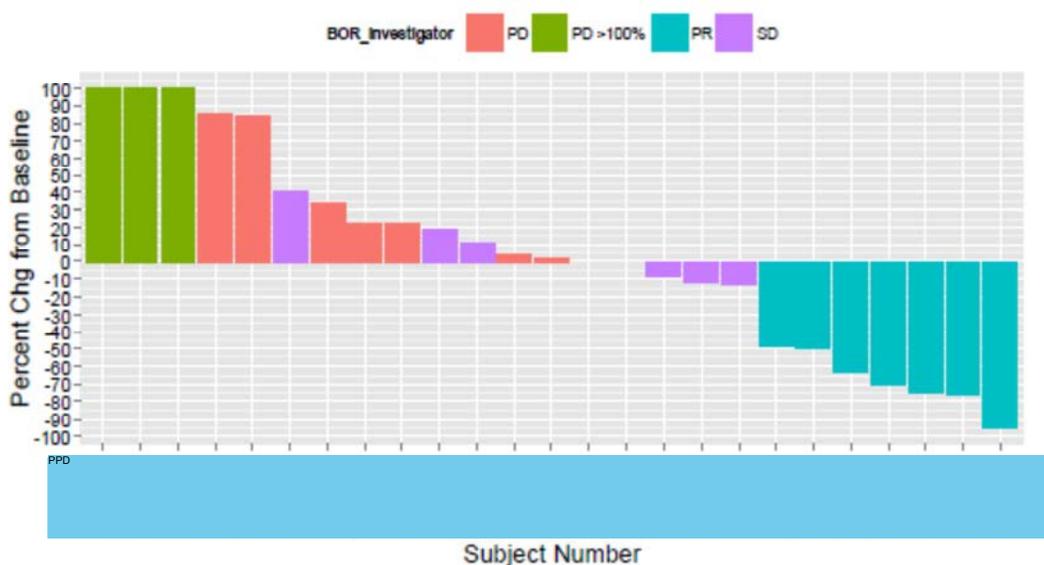


Figure 2 Best Percent Change from Baseline in Target Lesions by Best Objective Response (Full Analysis Set Population, by Investigator Assessment) KEYNOTE-012

For the individual patient, it is potentially possible that receiving a regimen such as gemcitabine/carboplatin earlier in the disease course may be better than receiving it later. However, in oncology, it has been uncommon to observe differences in overall disease outcomes based on the sequence of treatments. For example, patients initially allocated to a placebo treatment in a clinical trial and then crossed over to active treatment, in general, have an overall survival outcome similar to those first allocated to an active treatment.

Cross over in a clinical trial with a placebo arm represents a form of delayed treatment where the patient is first allocated to an ineffective treatment. However, in the majority of cases, such an approach does not have an adverse impact on patient outcomes. In fact, cross over is commonly prohibited in such clinical trials for the reason that receipt of treatment, whether

early or late in the disease course, yields a similar result, thus confounding a clinical trial designed to detect a difference between treatments. The observation of significant activity with pembrolizumab (MK-3475) further decreases the possibility that sequence of treatment could adversely impact the overall clinical course of a patient. These considerations suggest that it is reasonable to treat patients with pembrolizumab (MK-3475) before administering an alternative regimen such as gemcitabine/carboplatin.

In light of the relatively limited benefit from cytotoxic chemotherapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who cannot receive cisplatin, and the promising results with pembrolizumab (MK-3475) and other anti-PD-1 pathway agents [40], pembrolizumab (MK-3475) will be evaluated as monotherapy in this population.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010 and KN021), and three studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab (MK-3475) (200 mg Q3W) as 1L therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy. Objective response rate (ORR) based on RECIST 1.1 as assessed by independent radiology review will be used as the primary efficacy endpoint. The requirement that subjects have measurable disease will be assessed by the central vendor.

RECIST 1.1 will also be used by the local site to make treatment decisions. For this purpose, RECIST 1.1 will be adapted to account for the unique tumor response profile seen with treatment of pembrolizumab (MK-3475) (Refer to Section 5.2.2.1).

In the first line treatment of advanced/unresectable (inoperable) or metastatic urothelial cancer, response rates (RRs) generally observed with other single agents have ranged from 12%-28% [31; 41; 42; 43; 44; 45; 46]. The one exception was a study with paclitaxel where a RR of 42% was observed [47]. Despite the high RR with paclitaxel, the median duration of response approximated 7 months, where the median number of 3 week cycles administered in responding patients was 8. In addition, results in all of these studies were obtained in cisplatin eligible patients, rather than cisplatin ineligible patients who will be enrolled in this study. A limitation of the existing literature is a general lack of comparable information for cisplatin ineligible patients, thus necessitating reference to results with cisplatin eligible patients as the best source of data to provide context.

Results observed with pembrolizumab in bladder and other cancers have shown extended durations of response not typically observed with existing agents. Duration of response has been recognized as an important goal and is cited as one of the primary reasons for the use of, for example, IL-2 in renal cell carcinoma.

The RR results obtained in this trial will be compared to an historical RR of 30%. A 30% RR is at the high end of RRs observed with existing agents tested in the first line setting in populations actually more likely to respond than the cisplatin ineligible patients included in this trial. Considering the effect of pembrolizumab on duration of response and the population of cisplatin ineligible patients being studied, a RR of 30% is considered clinically important.

4.2.3.1.2 Secondary

PD L1 Expression

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab (MK-3475).

4.2.3.1.3 Exploratory

4.2.3.1.3.1 Patient Reported Outcomes

EORTC QLQ-C30, EQ-5D and Health Economic Assessment are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30

EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7 point scale scoring with anchors (1=very poor and 7=excellent). This assessment will be completed at various time points as specified in the study Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

eEuroQoL-5D

The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [48]. Each dimension has three levels: no problems, some problems, extreme problems. The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The eEQ-5D will always be completed by subjects first before completing the EORTC QLQ-C30 and is to be completed at various time points as specified in the study Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

Health Economic Assessment

The health economic assessment (HEA) form will be completed via an interview with the subject by qualified site personnel. The objective of the HEA form is for the site personnel to collect information from subjects on all the non-study related health care contacts made throughout the study. The HEA is to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 2 until 30 days post-treatment discontinuation.

4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab (MK-3475) in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer. 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 experienced by subjects who have received pembrolizumab (MK-3475), including serious adverse events (SAEs) and events of clinical interest (ECIs).

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 will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific 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.

4.2.3.3 Planned Exploratory Biomarker Research

Subjects will be required to have newly obtained core or excisional tumor biopsies (fine needle aspiration is not acceptable) of sufficient quality to support the secondary biomarker objective: “To investigate the correlation between PD-L1 protein expression by immunohistochemistry (IHC) and anti-tumor activity of pembrolizumab (MK-3475) as 1L therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy”. If a relationship between PD-L1 expression by IHC is found, a cut-point associated with optimal predictive value will be determined.

If needed, additional data from this trial may be used to supplement external data in order to determine a cut-point. In such a circumstance, the subject data utilized to supplement the external data will not be included in the data utilized to assess the primary endpoint in this trial and the sample size of the PDL1-positive population required for assessment of the primary endpoint will not be altered from that currently specified.

The tissue specimens will be evaluated at a central laboratory for expression status of PD-L1 in a retrospective analysis from subjects enrolled in the study, thus tissue availability, but not high biomarker expression is required for trial entry. Therefore, subjects will be enrolled onto this trial irrespective of PD-L1 expression (including subjects whose tumors do not express PD-L1). Additionally, if available, archived tumor tissue specimens from prior biopsies will be collected for determination of PD-L1 status to compare biomarker

expression in archived specimens against that in newly obtained tumor tissue that is collected as a requirement for entry into the trial. Previous unpublished data has suggested discordance between newly obtained and archived specimens. The collection of archived specimens will help determine if this limitation occurs with bladder cancer samples.

Tumor PD-L1 IHC results from NSCLC subjects treated with pembrolizumab (MK-3475) showed that pretreatment tumor PD-L1 expression was a statistically significant predictor of response. In subjects with evaluable tumor PD-L1 expression, confirmed responses by RECIST v1.1 (and immune related response criteria - irRC) occurred in subjects with tumors strongly positive for PD-L1 [49], suggesting that PD-L1 may be a predictive biomarker of anti-PD-1 activity. Recent preliminary data presented at the 2014 American Society of Clinical Oncology (ASCO) annual meeting demonstrated the value of PD-L1 expression in predicting response to MPDL3280a (Roche's anti-PDL1 antibody) in patients with urothelial cancer [40].

Additional biomarker research to identify factors important for pembrolizumab (MK-3475) therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this trial may undergo proteomic, genomic, metabolomic and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab (MK-3475) therapy and other immunologic targets.

Assays may include but are not be limited to:

Immunohistochemistry

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab (MK-3475). Other exploratory biomarkers (e.g. PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material (biopsy specimens, peripheral blood) will be completed to assess expression of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab (MK-3475). The hypothesis to be tested is that pembrolizumab (MK-3475) induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD-L1 & interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10). microRNA profiling may also be pursued in serum samples.

Proteomic analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab (MK-3475) therapy, as well as levels of PD-L1

IHC or protein in the tumor. Blood would be a less invasive compartment compared to tumor from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, Liquid chromatography/Mass Spectrometry. This approach could identify novel protein biomarker that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being ‘hypermuted’ or can detect the presence of specific T-cell clones within the tumor microenvironment or in the peripheral blood. There is a potential that the hypermuted state and/or increased T-cell clonality may correlate with response to pembrolizumab (MK-3475) therapy, and/or that the converse, ‘hypomuted’ state or lack of dominant T-cell clones may correlate with non-response.

In addition, understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population.

4.2.3.4 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. 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.

4.3 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/Female subjects of at least 18 years of age with advanced/unresectable (inoperable) or metastatic transitional cell cancer who are ineligible for cisplatin-based therapy 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/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have histologically or cytologically-confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed. Subjects with non-urothelial cancer of the urinary tract are not allowed.
4. Be considered cisplatin-ineligible to receive cisplatin-based combination therapy, based on having at least one of the following criteria:
 - a. ECOG performance status of 2 (the proportion of ECOG 2 subjects will be limited to approximately 50% of the total population)

- b. Creatinine clearance (calculated or measured) < 60 mL/min but \geq 30 mL/min

Note: Subjects with a creatinine clearance (calculated or measured) < 30 mL/min or on dialysis are excluded from the trial.

- c. CTCAE v.4, Grade \geq 2 audiometric hearing loss (25dB in two consecutive wave ranges)
- d. CTCAE v.4, Grade \geq 2 peripheral neuropathy
- e. NYHA Class III heart failure (Appendix 12.6)
5. Have received no prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer
- a. Adjuvant platinum based chemotherapy, following radical cystectomy, with recurrence > 12 months from completion of therapy is permitted
- b. Neoadjuvant platinum based chemotherapy, with recurrence > 12 months since completion of therapy is permitted.

Note: Low-dose chemotherapy (e.g., low dose cisplatin, cisplatin+5FU, mytomyacin+5FU, or cisplatin+paclitaxel) given concurrent with radiation to the primary tumor site is not considered as systemic therapy.

6. Have provided tissue for biomarker analysis from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (**mandatory**). Adequacy of the biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory.
7. Have measurable disease based on RECIST 1.1 as determined by central review. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale, as assessed within 10 days prior to treatment initiation.
9. Demonstrate adequate organ function as defined in [Table 1](#). All screening labs should be performed within 10 days of treatment initiation.

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	
Creatinine OR Measured or calculated ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN OR ≥30 mL/min for subjects with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT) or PTT	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
^a Creatinine clearance should be calculated per institutional standard. For subjects with a baseline calculated creatinine clearance below normal institutional laboratory values, a measured baseline creatinine clearance should be determined.	

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

11. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

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

12. Male subjects must 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.

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

5.1.3 Subject Exclusion Criteria

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

1. Has disease that is suitable for local therapy administered with curative intent.
2. 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 prior to the first dose of treatment.
3. Has had a prior anti-cancer monoclonal antibody (mAb) for direct anti-neoplastic treatment within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Subjects with neuropathy or \leq Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. A history of prostate cancer that was identified incidentally following cystoprostatectomy for bladder cancer is acceptable, provided that the following criteria are met: stage T2N0M0 or lower; and Gleason score \leq 6, and undetectable PSA.
6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable [without evidence of progression by imaging (confirmed by CT scan if CT used at prior imaging, or confirmed by MRI if MRI was used at prior imaging) for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline], have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
8. Has evidence of interstitial lung disease or active non-infectious pneumonitis.
9. Has an active infection requiring systemic therapy.
10. 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.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).
15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Has received a live virus vaccine within 30 days of planned start of trial treatment.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in [Table 2](#).

Table 2 Trial Treatment

Drug, Vaccine, Biologic, Device, etc.	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
pembrolizumab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

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)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification and Toxicity Management Guidelines

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 3](#).

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:				
<ol style="list-style-type: none"> 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. 3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. 				
Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects 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	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor subjects 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). • Subjects with \geq Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects 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	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia 	<ul style="list-style-type: none"> Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids and initiate hormonal replacements as clinically indicated. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Based on severity of AE administer corticosteroids 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Based on type and severity of AE administer corticosteroids 	<ul style="list-style-type: none"> 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		
<p>1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.</p> <p>NOTE: For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to \leq Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).</p>				

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 4](#).

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<p>Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated</p>	<p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p>	<p>None</p>
<p>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</p>	<p>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</p>	<p>Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).</p>

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<p>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</p>	<p>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.</p>	<p>No subsequent dosing</p>
<p>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</p>		

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 subject's study record.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Trial treatments will be administered on an outpatient basis, unless the subject is hospitalized for an unrelated reason .

5.2.2.1 Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Treatment cycle intervals may be increased due to toxicity as described in

Section 5.2.1.2. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab (MK-3475) dose calculation, reconstitution, preparation of the infusion fluid, and administration.

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

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects will be assigned to pembrolizumab (MK-3475) in an unblinded fashion.

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

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the 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 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab (MK-3475)
- Radiation therapy
 - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Subjects who require corticosteroids to manage drug-related adverse events must be at an equivalent dose of ≤ 10 mg per day of prednisone to resume dosing with MK-3475. Furthermore, an inability to reduce the corticosteroid dose for managing a drug-related adverse event to the equivalent of ≤ 10 mg prednisone per day within 12 weeks of last MK-3475 dose should prompt discussion between the investigator and Sponsor regarding the subject's ability to continue on treatment in the trial.
 - Note: Temporary use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye or transfusions) is permitted.
 - Note: Use of intermittent inhaled steroids or local injection of corticosteroids is permitted upon consultation with the sponsor.

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.

The Exclusion Criteria describes other medications, which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events 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 intravenous 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 the event 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 dose modification.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (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 is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. 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).

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

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-Reporting of Pregnancy and Lactation to the Sponsor. 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 pembrolizumab (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 pembrolizumab (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.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a

subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

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.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, please see Section 5.8.1.

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 5.8.1 below.

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab (MK-3475)

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab (MK-3475) after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.

- 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). After the end of treatment, 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 treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier, as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease 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 overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Treatment after initial evidence of radiologic disease progression

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by reactivating endogenous cancer-specific immune responses, which may be functionally exhausted. The response patterns seen with such therapies may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide an accurate or complete response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Therefore, RECIST 1.1 will be used with the following adaptation:

If radiologic imaging by local/site assessment shows PD, tumor assessment may be repeated by the site ≥ 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows SD, PR or CR, treatment may be continued as per treatment calendar. If repeat imaging still meets the threshold for PD ($\geq 20\%$ increase in tumor burden compared to nadir) but shows a reduction in tumor burden compared to the previous time point, treatment may be continued as per treatment calendar after consultation with Sponsor. If repeat imaging confirms progressive disease without reduction in tumor burden compared to the previous time point, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual).

The decision to continue study treatment after the 1st evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in [Table 5](#) below. Confirmatory imaging maybe performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point (every 42 days \pm 7 days) may be used as confirmation. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- Subjects exhibiting toxicity from trial therapy as outlined in Section 5.2.1.2 and 7.2 may NOT continue to receive trial therapy.

Table 5 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1 st radiologic evidence of PD	Repeat imaging at \geq 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at \geq 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD (no reduction in tumor burden from prior scan)	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan confirms PD (reduction in tumor burden from prior scan)	Continue regularly scheduled imaging assessments	Continue study treatment after consultation with Sponsor	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator and Sponsor's discretion
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan (as assessed by the investigator/site radiologist), an exception may be considered to continue treatment upon consultation with the Sponsor.

Additional information is included in the Site Imaging Manual.

5.8.2 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab (MK-3475) and had at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab (MK-3475) at the discretion of the investigator if no cancer treatment was administered since the last dose of

pembrolizumab (MK-3475), the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1. Response or progression in this Second Course Phase will not count towards the ORR as the primary endpoint in this trial.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

Trial Period:	Screening Phase			Treatment Cycles ^a						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)			1	2	3	4	To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits ^b	Survival Follow-up ^c
Scheduling Window (Days) ^d :	Any time ^e to -1	-28 to -1	-10 to -1	+3 ^d	± 3	± 3	± 3	5	6				
Administrative Procedures													
Informed Consent	X ^e												
Informed Consent for Future Biomedical Research	X ^f												
Inclusion/Exclusion Criteria		X											
Subject Identification Card	X												
Demographics and Medical History		X											
Prior and Concomitant Medication Review ^g		X		X	X	X	X	X	X	X	X		
Obtain randomization number and study drug assignment using IVRS/IWRS				X ^d									
Pembrolizumab (MK-3475) Administration				X ^d	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X ^c
Survival Status ^c				←----->									X ^c
Clinical Procedures/Assessments													
Review Adverse Events ^{h, 1}		X		X	X	X	X	X	X	X	X	X ⁱ	X ⁱ
12-Lead Electrocardiogram (Locally performed)		X											
Full Physical Examination ^j		X											
Directed Physical Examination ^j				X	X	X	X	X	X	X			
Vital Signs, Weight and Height ^k		X		X	X	X	X	X	X	X	X	X	X
ECOG Performance Status ^l			X	X	X	X	X	X	X	X	X	X	X

Trial Period: Treatment Cycle/Title:	Screening Phase			Treatment Cycles ^a						End of Treatment	Post-Treatment		
	Screening (Visit 1)			1	2	3	4	To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits ^b	Survival Follow-up ^c
	Any time ^e to -1	-28 to -1	-10 to -1	+3 ^d	± 3	± 3	± 3	5	6				
Scheduling Window (Days) ^d :										At time of discon	30 days post last dose (± 3 days)	Every 6 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG ^m			X ^m										
PT/INR and aPTT ⁿ			X ^o										
CBC with Differential ^p			X ^o		X	X	X	X	X	X	X ^q		
Chemistry Panel ^p			X ^o		X	X	X	X	X	X	X ^q		
Urinalysis ^p			X ^o		X		X		X		X ^q		
T3, FT4 and TSH ^p			X ^o		X		X		X		X ^q		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory													
Blood for serum and plasma for Correlative Studies ^f				X									
Whole blood sample for RNA/DNA for Correlative Studies ^s				X	X	X				X			
Blood for Genetics ^t				X									
Efficacy Measurements													
Tumor Imaging		X ^u					X ^v		X ^v	X ^w		X ^b	
Tumor Tissue Collection													
Newly Obtained (required) and Archival (if available) Tissue Collection for biomarker analysis ^x	X ^x												
Patient Reported Outcomes													
EuroQol EQ-5D				X ^y	X ^y	X ^y	X ^y		X ^y	X ^y	X ^y		
EORTC QLQ-C30				X ^y	X ^y	X ^y	X ^y		X ^y	X ^y	X ^y		
Health Economic Assessment (HEA)					X ^y	X ^y	X ^y		X ^y	X ^y	X ^y		

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule. Imaging should be performed at 9 weeks (63 ± 7 days) after the first dose of trial treatment on Day 1 Cycle 1, and every 6 weeks thereafter (42 days ± 7 days) regardless of any treatment delays. After 12 months, imaging frequency should be reduced to every 12 weeks (84 ± 7 days).

Trial Period:	Screening Phase			Treatment Cycles ^a						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)			1	2	3	4	To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits ^b	Survival Follow-up ^c
								5	6				
Scheduling Window (Days) ^d :	Any time ^e to -1	-28 to -1	-10 to -1	+3 ^d	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 6 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
<p>b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (42 ± 7 days) in the first year and every 12 weeks (84 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the investigator/site radiologist, (3) death, or (4) the end of the study, whichever occurs first.</p> <p>c. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).</p> <p>d. In general, the window for each visit is ± 3 days unless otherwise noted. Study personnel will access IVRS/IWRS to obtain randomization number and study drug assignment. Cycle 1 treatment must be given within 3 days of randomization number assignment in IVRS/IWRS.</p> <p>e. Written informed consent must be obtained prior to performing any protocol specified procedure. Please note there is no specific study window for acquiring the “newly obtained” tissue specimen and it may be obtained any time before the first dose of study drug, as long as the subject has not received any intervening systemic therapy from the time the tissue was collected until the time the subject enters the study.. Written consent should be obtained prior to acquiring the biopsy specimen for the study. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the window specified for screening procedures (e.g., within 28 days for tumor imaging assessments or within 10 days the first dose of trial treatment for required lab tests). Screening number will be assigned when the study informed consent is signed.</p> <p>f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.</p> <p>g. Prior medications – Record all medications taken within 30 days of Cycle 1. 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.</p> <p>h. 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.</p> <p>i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.</p> <p>j. Full PE at screening visit; Direct PE for all other visits.</p> <p>k. Vital signs to 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 every cycle, at treatment discontinuation, and at follow-up.</p> <p>l. ECOG performance status at screening to be performed within 10 days prior to Day 1 of Cycle 1. ECOG performance status will also be performed prior to the administration of each dose of trial treatment at every cycle, at treatment discontinuation, and at follow-up.</p> <p>m. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to 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.</p> <p>n. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.</p> <p>o. Laboratory tests for screening are to be performed within 10 days prior to Day 1 of Cycle 1. See Section 7.1.3 for details regarding laboratory tests.</p> <p>p. After Cycle 1, predose lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests (T3, FT4 and TSH) and urinalysis should be repeated every 2 cycles after Cycle 6 up to one year of treatment. CBC and Chemistry tests should be collected predose on Day 1 of <u>every</u> 3 week cycle after Cycle 6. For subjects with a baseline estimated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed. See Section 7.1.3 for details regarding laboratory tests. A persistent elevated alkaline phosphatase should prompt consideration for the presence of bony metastatic disease.</p> <p>q. Unresolved abnormal labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.</p>													

Trial Period:	Screening Phase			Treatment Cycles ^a						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)			1	2	3	4	To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits ^b	Survival Follow-up ^c
	5	6											
Scheduling Window (Days) ^d :	Any time ^e to -1	-28 to -1	-10 to -1	+3 ^d	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 6 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
<p>r. Blood for serum and blood for plasma correlative studies is to be collected only predose at Cycle 1. See Procedures Manual. Any leftover samples from the correlative blood studies will be stored for future biomedical research if the subject signs the FBR consent</p> <p>s. Whole blood sample for RNA/DNA correlative studies should be collected predose at Cycles 1, 2, and 3, and again at treatment discontinuation.. See Procedures Manual. Any leftover samples from the correlative blood studies will be stored for future biomedical research if the subject signs the FBR consent.</p> <p>t. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.</p> <p>u. The initial tumor imaging at screening will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. Measureable disease based on RECIST 1.1 must be confirmed by central review before enrollment. All subjects will have a baseline bone scan performed at screening. Bone scans at baseline must be sent to central imaging vendor for review with initial tumor imaging to determine eligibility. Subjects with positive bone scans at baseline will be followed with additional scans performed at 9 weeks (± 7 days) after the first dose of trial treatment on Day 1 Cycle 1, and then every 6 weeks (± 7 days) thereafter or more frequently if clinically indicated. For subjects with new symptoms suggestive of osseous metastasis, a bone scan should be obtained. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations. Refer to Section 7.1.2.6.3 of the protocol and site imaging manual.</p> <p>v. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after the first dose of trial treatment on Day 1 Cycle 1, and then every 6 weeks (± 7 days) thereafter or more frequently if clinically indicated. After 12 months, imaging frequency should be reduced to every 12 weeks (± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a subject throughout the trial. On-study scans should be submitted immediately to the central imaging vendor; and progressive disease should be confirmed by the investigator/site radiologist prior to subject discontinuation from trial.</p> <p>w. In subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.</p> <p>x. Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy (FNA not adequate) (mandatory) must be provided to the central vendor prior to randomization number assignment, and an archival tissue sample (if available) will also be collected. Adequacy of the biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory before enrollment. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.</p> <p>y. For electronic patient reported outcomes (ePROs) it is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. ePROs are to be administered starting with EQ-5D, followed by EORTC QLQ-C30, and HEA. Health economic assessment (HEA) to be completed by trained personnel prior to all other study procedures. All ePROs are to be performed prior to Cycle 1, Cycle 2, Cycle 3, Cycle 4 and every 2 cycles thereafter (e.g., Cycle 6, Cycle 8, Cycle 10) up to a year or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit. If the subject does not completed the ePROs the MISS MODE form must be completed to capture the reason the assessment was not performed.</p>													

6.2 Second Course Phase (Retreatment)

Trial Period:	Treatment Cycles ^a						End of Treatment	Post-Treatment		
	1	2	3	4	To be repeated beyond 6 cycles			Discon	Safety Follow-up	Follow Up Visits ^b
5					6					
Treatment Cycle/Title:										
Scheduling Window (Days) ^d :	+3 ^d	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 6 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
Administrative Procedures										
Eligibility Criteria ^e	X									
Concomitant Medication Review ^f	X	X	X	X	X	X	X	X		
Pembrolizumab (MK-3475) Administration ^g	X	X	X	X	X	X				
Post-study Anticancer Therapy Status									X	X ^e
Survival Status ^e	←----->									X ^e
Clinical Procedures/Assessments										
Review Adverse Events ^h	X	X	X	X	X	X	X	X ⁱ	X ⁱ	
Full Physical Examination ^j	X									
Directed Physical Examination ^l		X	X	X	X	X	X			
Vital Signs and Weight ^k	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory										
Pregnancy Test – Urine or Serum β-HCG ^l	X									
PT/INR and aPTT ^m	X ⁿ									
CBC with Differential ^o	X ⁿ	X	X	X	X	X	X	X ^r		
Chemistry Panel ^o	X ⁿ	X	X	X	X	X	X	X ^r		
Urinalysis	X ⁿ									
T3, FT4 and TSH ^o	X ⁿ		X		X			X ^r		
Efficacy Measurements										
Tumor Imaging ^p	X		X		X		X ^q		X ^b	

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule. Imaging should always be performed every 6 weeks (42 days ± 7 days) regardless of any treatment delays. After 12 months, imaging frequency should be reduced to every 12 weeks (± 7 days).

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (+7 days) in the first year and every 12 weeks (± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the investigator/site radiologist, (3) death, or (4) the end of the study, whichever occurs first.

Trial Period:	Treatment Cycles ^a						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	1	2	3	4	To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits ^b	Survival Follow-up ^c
					5	6				
Scheduling Window (Days) ^d :	+3 ^d	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 6 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)

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

d. In general, the window for each visit is ± 3 days unless otherwise noted.

e. Subjects who either a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab (MK-3475) for reasons other than disease progression or intolerance may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.1.

f. 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.

g. Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation.

h. 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.

i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.

j. Full PE at Cycle 1; Directed PE for all other visits.

k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only. Vital signs will be collected prior to the administration of each dose of trial treatment at every cycle, at treatment discontinuation, and at follow-up.

l. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of the retreatment phase. 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.

m. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.

n. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab (MK-3475). See Section 7.1.3 for details regarding laboratory tests.

o. After Cycle 1, predose lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests (T3, FT4 and TSH) should be repeated every 2 cycles after Cycle 5 up to one year of treatment. CBC and Chemistry tests should be collected predose on Day 1 of every 3 week cycle after Cycle 6. See Section 7.1.3 for details regarding laboratory tests. A persistent elevated alkaline phosphatase should prompt consideration for the presence of bony metastatic disease.

p. A scan must be performed within 28 days prior to restarting treatment with pembrolizumab (MK-3475). Imaging should continue to be performed every 6 weeks (42 ± 7 days) from the first retreatment dose or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. On-study scans should be submitted immediately to the central imaging vendor; and progressive disease should be confirmed by the investigator/site radiologist prior to subject discontinuation from trial.

q. In subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.

r. Unresolved labs for drug related AEs should be followed until resolution. Labs do not need to be repeated at the end of trial treatment if labs are within normal range.

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.

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.

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the subject's urothelial cancer will be recorded separately and not listed as medical history.

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's urothelial cancer.

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 30 days before starting the trial. Prior treatment for urothelial cancer will be recorded separately and not listed as a prior medication.

7.1.1.5.1.1 Prior Treatment Details for Urothelial Cancer

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5.2.1 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

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.

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

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

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after treatment allocation. 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.

All subjects will be assigned a randomization number, however all subjects will receive the same pembrolizumab (MK-3475) 200 mg every three weeks (Q3W) as trial treatment by non-random assignment in unblinded fashion.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab (MK-3475) doses 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. The total volume of pembrolizumab (MK-3475) infused will be compared to the total volume prepared to determine compliance to each dose of pembrolizumab (MK-3475) administered. The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual.

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 events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 12.7). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab (MK-3475) all AEs of unknown etiology associated with pembrolizumab (MK-3475) exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in the administrative binder regarding the identification, evaluation and management of potential irAEs.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. 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 at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix 12.5) at screening, prior to dosing on Day 1 of each treatment cycle and at discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central vendor can be found in the imaging section of the Site Imaging Manual (SIM). Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. Bone scans will also be utilized to assess osseous metastases. Additionally, plain X-ray evaluation will be obtained for symptomatic sites with negative bone scan evaluations.

Real-time determination of measurable disease by central review at screening will be used to determine subject eligibility. The central imaging vendor will receive all images at the timepoints specified in the Study Flow Chart from the sites. Real-time determination of measurable disease by central review at screening will be used to determine subject eligibility. The central imaging vendor will receive all images at the timepoints specified in the Study Flow Chart from the sites. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor as well.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the first dose of trial treatment. The central imaging vendor must review the baseline scan to determine subject eligibility per RECIST 1.1. The baseline imaging scan should be submitted to the central imaging vendor immediately. Bone scans will be performed at baseline for all subjects. Bone scans at baseline must be sent to central imaging vendor immediately for review with initial tumor imaging to determine eligibility.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality, meet the requirements specified in the imaging manual, and performed within 28 days prior to the first dose of trial treatment. Subjects who enter the study with stable brain metastases should continue to have brain imaging as clinically indicated.

7.1.2.6.2 Tumor Imaging During Trial

The first imaging assessment should be performed at 9 weeks (63 days \pm 7 days) after the first dose of trial treatment on Day 1 Cycle 1. Subsequent imaging should be performed every 6 weeks (42 days \pm 7 days), more frequently if clinically indicated. Subjects who remain on treatment for a year will have imaging performed every 12 weeks (84 \pm 7 days). Imaging should not be delayed for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle intervals.

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (6 weeks later), whichever is clinically indicated.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the SPONSOR, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 5.8.1.

7.1.2.6.3 Bone Scans

Bone scans will be performed at baseline for all subjects. Bone scans at baseline must be sent to central imaging vendor for review with initial tumor imaging to determine eligibility. Subjects with positive bone scans at baseline will be followed with additional scans performed at 9 weeks (\pm 7 days) after the first dose of trial treatment on Day 1 Cycle 1, and then every 6 weeks (\pm 7 days) thereafter or more frequently if clinically indicated. Subjects with new symptoms concerning of osseous metastasis (e.g., new persistently elevated alkaline phosphatase) a bone scan should be obtained. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations. New osseous

uptake, upon confirmation with CT or per institutional standard, will be assessed for progression per RECIST 1.1. Lytic/mixed lesions with soft tissue component may be included in the evaluation of disease burden if it meets measurability criteria, while blastic lesions are considered non-measurable, in accordance with RECIST 1.1.

7.1.2.6.4 Assessment of Disease

For the purposes of the primary study endpoints, RECIST 1.1 (Appendix 12.8) will be applied by the central imaging vendor as the primary measure for assessment of tumor response. All scans, including confirmatory scans, should be submitted to the central imaging vendor for retrospective evaluation and should be submitted in a timely fashion.

Sites should also assess tumor response and progression per modified RECIST and this data will be collected in the clinical database. Site assessment of tumor response and progression will be used for all subject decision making in the trial. Subjects who have unconfirmed progressive disease will be managed as detailed in Section 5.8.1, and these criteria may be applied at the discretion of the investigator.

Imaging during the follow-up period is to be repeated every 6 weeks (42 ± 7 days), or every 12 weeks (84 ± 7 days) after the first year following the initiation of trial therapy, for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new anti-neoplastic therapy.

Review by the central imaging vendor based on RECIST 1.1 will be used to determine subject eligibility. Confirmatory scans performed per modified RECIST will be evaluated by local reading for the purpose clinical decision-making. Real-time analysis of subject eligibility by RECIST 1.1 will be conducted. Retrospective analysis of treatment response by RECIST 1.1 and modified RECIST will also be performed by a central imaging vendor.

7.1.2.7 Tumor Tissue Collection and Correlative Blood Sampling

A “newly obtained” core or excisional biopsy (fine needle aspirate not adequate) must be submitted to a central lab for characterization of PD-L1 expression. PD-L1 expression will be evaluated retrospective in this trial. The tumor tissue must be received by the central vendor and be deemed adequate for evaluation prior to subject randomization number assignment.

The “newly obtained” tissue sample may be obtained at any time before the first dose of study drug, as long as the subject has not received any intervening systemic therapy from the time the tissue was collected until the time the subject enters the study.

Participation in this trial will be dependent upon supplying tumor tissue from locations not radiated prior to biopsy. Biopsies obtained PRIOR to receipt of neoadjuvant/adjuvant chemotherapy is NOT permitted. Subjects who received neoadjuvant/adjuvant therapy are permitted onto the trial as long as therapy was completed at least 12 months prior to the diagnosis of metastatic disease. Only tumor specimens obtained AFTER completion of the neoadjuvant/adjuvant therapies, and only AFTER metastatic or muscle invasive disease is observed will be used to assess PD-L1 status.

If a tumor biopsy is to be obtained from an intended target lesion during eligibility assessment, the biopsy should be performed prior to obtaining the baseline scan. Otherwise, a new baseline scan should be obtained.

Additionally, if available, archived tumor tissue specimens from prior biopsies will be collected for determination of PD-L1 status to compare biomarker expression in archived specimens against the in newly obtained tumor tissue that is collected as a requirement for entry into the trial.

Whole blood sample for RNA/DNA correlative studies should be collected predose at Cycles 1, 2, and 3, and again at treatment discontinuation. Blood for serum and blood for plasma correlative studies is to be collected only predose at Cycle 1.

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

7.1.2.8 Patient Reported Outcomes (PROs)

The EuroQol EQ-5D and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by subjects in the following order: EuroQol EQ-5D first then EORTC QLQ-C30 at the time points specified in the Trial Flow Chart. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic.

The health economic assessment (HEA) form will be completed via an interview with the subject by qualified site personnel after the subject completes all other questionnaires. The form captures all non-study related health care contacts made throughout the study

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in [Table 6](#).

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin (β -hCG) ^a
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential) ^d	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) (or Free T3) ^b
Red Blood Cell Count	Carbon dioxide (CO ₂ or bicarbonate) ^b	Microscopic exam, if abnormal results are noted	Free tyroxine (Free T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test ^a	Thyroid Stimulating Hormone (TSH)
Absolute Lymphocyte Count	Chloride		PK for pembrolizumab (MK-3475)
	Creatinine ^c (GFR can also be used in place of creatinine or CrCl)		Anti-pembrolizumab (MK-3475) Antibodies
	Glucose		Blood for correlative studies
	Phosphorus		Blood for FBR
	Potassium		Blood for Genetics
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen ^e		
	Uric acid		
<p>^a Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.</p> <p>^b If considered standard of care in your region</p> <p>^c For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.</p> <p>^d For WBC results Absolute or % acceptable per their institutional standard.</p> <p>^e Blood Urea Nitrogen is preferred; if not available urea may be tested</p>			

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. The results from thyroid function tests (T3/or FT3, FT4, and TSH) are not required to be available nor reviewed prior to each dose of trial treatment after Cycle 1, unless clinical suspicion of thyroid dysfunction is observed.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, upon a approval of Amendment 3, each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 3 may be stored only at this time. Analysis will be performed if required.

7.1.3.3 Future Biomedical Research

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

- Leftover DNA for future use
- Leftover tumor tissue
- Leftover biomarker samples

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab (MK-3475) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or 24 months of treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.3.2) . .

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Pharmacy Manual and Site Imaging Manual.

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

Approximately 28 days prior to randomization number assignment, 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.

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

frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Informed Consent Form (ICF) signed prior to completing any protocol specified procedure.
- Laboratory tests and evaluation of ECOG status are to be performed within 10 days prior to the first dose of trial treatment
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Initial tumor imaging must be performed within 28 days of the first dose of study.
- A “newly obtained” tissue sample may be obtained at any time before the first dose of study drug, as long as the subject has not received any intervening systemic therapy from the time the tissue was collected until the time the subject enters the study. See Section 7.1.2.7 for additional details regarding tumor tissue requirements.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Treatment Period/Vaccination Visit

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

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab (MK-3475) with SD or better may be eligible for up to one year of additional pembrolizumab (MK-3475) therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
 - Stopped initial treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
 - Was treated for at least 24 weeks with pembrolizumab (MK-3475) before discontinuing therapy
 - Received at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared

OR

- Subject had SD, PR or CR and stopped pembrolizumab (MK-3475) treatment after 24 months of trial treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab (MK-3475)
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab (MK-3475)
- Have a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrate adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

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

- Male subjects 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.

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

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

7.1.5.3 Post-Trial

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (\pm 3 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade $>$ 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. 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.

Subjects who are eligible for retreatment with pembrolizumab (MK-3475) (as described in Section 7.1.5.2.1) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (84 ± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression determined by the investigator/site radiologist, death, end of study, or if the subject begins retreatment with pembrolizumab (MK-3475) as detailed in Section 7.1.5.2.1. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab (MK-3475) according to the criteria in Section 7.1.5.2.1 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment with pembrolizumab (MK-3475).

7.1.5.3.3 Survival Follow-up

Once a subject stops receiving trial treatment, they will be followed for survival. Initially these data will be collected at the Safety Follow-up visit and 3-month Follow-up visits, and any subsequent visits for imaging that may occur until PD is confirmed or starting a new anti-cancer therapy. Once the subject stops the imaging assessments for this protocol every 6 weeks or then every 12 weeks (84 ± 7 days) after 1 year (e.g. for PD or starting a new anti-cancer therapy), the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (\pm 7 days) to assess for survival status, until death, withdrawal of consent, or end of the study, whichever occurs first. Post-study treatments and the subject's response to them will also be collected.

7.1.5.4 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in

section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose of pembrolizumab (MK-3475) will be defined as 1,000 mg or greater ($\geq 5x$ the indicated dose) No specific information is available on the treatment of overdose of pembrolizumab (MK-3475). 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 by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

(Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. 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 an other important medical event

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

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

Refer to [Table 7](#) for additional details regarding each of the above criteria.

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

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

guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

3. Additional adverse events:

A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the SPONSOR **within 24 hours** of the event, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines and either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 7 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 mild 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 of hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	† Results in death ; or	
	† Is life threatening ; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a new cancer (that is not a condition of the study) (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 Trial Governance and Oversight

7.3.1 Scientific Advisory Committee

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes made to primary and/or key secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

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).

The primary and secondary objectives of this study include evaluations of the clinical efficacy of pembrolizumab (MK-3475) as 1L therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy, in all subjects, PD-L1 positive, and PD-L1 strongly positive (if applicable) populations, by objective response rates, response duration, PFS, and OS. The PD-L1 positive/negative population is defined as patients with PD-L1 IHC assay CPS score of at least/lower than the pre-specified PD-L1 positive cut-point of 1%. The PD-L1 strongly positive is defined as patients with CPS score of at least the PD-L1 strongly positive cut-point determined using the biomarker discovery population (first 100 enrolled excluding subjects not evaluable). If a PD-L1 strongly positive cut-off with clinical utility cannot be determined, only the all subjects and PD-L1 positive populations will be evaluated.

Analyses examining the association between PD-L1 expression and clinical efficacy to determine PD-L1 cut-point determination will be discussed in 8.2.5.3. The biomarker discovery population consists of the first 100 subjects enrolled; data from the biomarker discovery population will not contribute to efficacy evaluations for the PD-L1 strongly positive population.

8.1.1 Efficacy Analyses

The all-patients-treated (APT) population will serve as the primary population for the analyses of efficacy data in this trial. ORR based on RECIST 1.1 assessed by independent radiology review is the primary efficacy endpoint. A point estimate and a 95% confidence interval (as determined by the upper and lower 97.5% one-sided confidence bounds) based on the exact binomial distribution will be provided in all subjects, PD-L1 positive, and PD-L1 strongly positive populations. No hypothesis testing will be performed. An outline of the efficacy analysis strategy is presented in [Table 8](#).

8.1.2 Safety Analyses

The APT population will be used for safety analyses. Safety will be summarized for all subjects treated.

8.1.3 Power and Sample Size

The sample size of this study is driven by the requirement for adequate efficacy evaluation for the PD-L1 strongly positive population. It is expected that ~350 subjects will be enrolled, which will provide enough subjects for the PD-L1 strongly positive population.

8.1.4 Biomarker/Interim Analysis

The biomarker analysis to establish the PD-L1 strongly positive cutpoint is planned. An interim futility analysis is planned for the PD-L1 negative population within the biomarker discovery population. See 8.2.9 for more details.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the clinical biostatistics department of the SPONSOR.

This trial is being conducted as an open-label non-randomized single-arm clinical trial. The trial has primary objectives in the subset of subjects that is PD-L1 positive, defined as a PD-L1 CPS score $\geq 1\%$, and PD-L1 strongly positive, defined as the PD-L1 CPS score \geq the optimal cut-point determined from data obtained from the biomarker discovery population. The study team will remain blinded to PD-L1 scores for individual patients throughout the study period until database lock for the primary study report; interim analyses related to PD-L1 scores will be conducted by a sponsor unblinded statistician.

The clinical biostatistics department will generate the allocation schedule for study treatment assignment. Allocation will be implemented in an interactive voice response system (IVRS).

8.2.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0. There is no hypothesis and the efficacy objectives are related only to estimation.

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

8.2.3.1 Efficacy Endpoints

The primary efficacy endpoint is objective response rate (ORR), defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) using RECIST 1.1 criteria assessed by independent radiology review at any time during the study.

Secondary efficacy endpoints include:

- Duration of response (DOR) (RECIST 1.1 by independent radiology review).
- Overall survival (OS) and progression free survival (PFS) (RECIST 1.1 by independent radiology review).
- PFS (RECIST 1.1 by independent radiology review) rate and OS rate at 6 months and 12 months.

8.2.3.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.2.

The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received MK-3475, including serious adverse events (SAEs) and events of clinical interest (ECIs). Immune-related ECIs, as described in Section 7.2.3.2, will be collected. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Population

The APT population, which consists of all enrolled subjects who receive at least one dose of study treatment, will serve as the primary population for the analyses of efficacy data in this trial. Supportive analyses of efficacy will be conducted in the full analysis set (FAS) population, which consists of all enrolled subjects who receive at least one dose of study treatment and have measureable disease at baseline.

The biomarker discovery population, subjects in this trial used for the determination of the PD-L1 strongly positive cut-point, will be excluded from efficacy analyses for the PD-L1 strongly positive population. These subjects will still be included in the efficacy analyses for all and PD-L1 positive subjects.

8.2.4.2 Safety Analysis Population

The APT population will be used for the analysis of safety data. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

8.2.4.3 Biomarker Discovery Population

The biomarker analysis will be based on all subjects within the first 100 enrolled by time that are deemed clinically evaluable, which is defined as any subjects who received at least one dose of study drug and had week 9 and week 15 scans, or discontinued due to radiographic/clinical progression or death before reaching week 15. The biomarker discovery population will be identified through routine review of accumulating data.

8.2.5 Statistical Methods

Statistical methods for efficacy and safety analyses are described in sections 8.2.5.1 and 8.2.5.2, respectively.

8.2.5.1 Statistical Methods for Efficacy Analyses

Efficacy will be available for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects. The first 100 study subjects (biomarker discovery population) will be evaluated for biomarker cut-point determination. The biomarker discovery population will be excluded from the primary and secondary objectives for the PD-L1 strongly positive subjects.

For the primary efficacy endpoint, the ORR based on RECIST 1.1 by independent radiology review, the point estimate, and 95% confidence interval (as determined by the upper and lower 97.5% one-sided confidence bounds) will be provided using an exact binomial distribution (Clopper and Pearson method). Subjects without response data will be counted as non-responders.

Duration of responses (DOR) based on RECIST 1.1 by independent radiology review will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a complete response or partial response will be included in this analysis. For PFS and OS, Kaplan-Meier (KM) curves, median estimates, and survival rates at 6 and 12 months based on the KM curves (95% CI is based on Greenwood's formula) will be

provided. Subjects without efficacy evaluation data or without survival data will be censored at Day 1.

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in [Table 8](#).

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The 95% confidence interval for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 3-5 AEs will be provided.

8.2.5.3 Statistical Methods for Biomarker Analyses

The evaluation of a general positive association between CPS and ORR will be investigated via standard logistic regression as well as generalized additive models. The potential to achieve a cut-off greater than CPS = 1% for defining a PD-L1 strongly positive population will involve a review of how the positive predictive value (PPV, response rate in those above a cut-off), negative predictive value (NPV, non-response rate in those below the cut-off), and fraction of patients defined as strongly positive change as a function of increasing cut-offs and whether there is evidence for a relative improvement in clinical utility relative to the 1% CPS cut-off. A PD-L1 strongly positive cut-off that maintains high NPV (e.g. near or above 90%) while achieving meaningful enrichment of response and largely capturing patients showing durable clinical benefit is sought. The profiles of PPV, NPV, and the percentage of patients above a given cut-off along with intervals quantifying the uncertainty in those profiles will be estimated as a function of potential cut-offs. Receiver operating characteristic curve analysis will also be used to understand the sensitivity and specificity profile and examine cut-offs that might be suggested based on the ROC curve and their appropriateness with regard to PPV and NPV. CPS ranges for any promising cut-offs will also have to be gauged in the context of practical implementation and interpretation by pathologists in clinical practice.

Table 8 Analysis Strategy for Efficacy Endpoints

Endpoint/Variable [‡] (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives:			
RECIST1.1 ORR by independent radiology review for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects	Exact method based on binomial distribution	APT/FAS	Subjects with missing data are considered non-responders
Secondary Objectives:			
Duration of Response, RECIST1.1 by independent radiology review, for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects	Summary statistics /Kaplan-Meier method	APT/FAS	Non-responders are excluded in analysis
Progression-free survival, RECIST1.1 by independent radiology review, for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects	Summary statistics /Kaplan-Meier method	APT/FAS	Censored at last assessment
Overall survival, for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects	Summary statistics /Kaplan-Meier method	APT/FAS	Censored at last assessment
95% confidence interval is determined by the upper and lower 97.5% one-sided confidence bounds.			

8.2.5.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.4.1 Demographic and Baseline Characteristics

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

8.2.6 Multiplicity

This is an estimation study. 95% confidence intervals of ORR will be provided. No multiplicity adjustment will be applied.

8.2.7 Sample Size and Power Calculation

The sample size is driven by the primary efficacy estimation for PD-L1 strongly positive subjects. [Table 9](#) and [Table 10](#) shows 95% CIs at different true ORR rates (number of events), for 60 and 75 PD-L1 strongly positive subjects, respectively.

Table 9 Estimates and 95% CIs with 60 PD-L1 Strongly Positive Subjects

Sample Size	Number of ORR Event	Proportion	Lower Limit	Upper Limit	Width of 95% CI
60	12	0.2	0.108	0.323	0.215
60	13	0.217	0.121	0.342	0.221
60	14	0.233	0.134	0.36	0.227
60	15	0.25	0.147	0.379	0.231
60	16	0.267	0.161	0.397	0.236
60	17	0.283	0.174	0.414	0.24
60	18	0.3	0.188	0.432	0.244
60	19	0.317	0.203	0.45	0.247
60	20	0.333	0.217	0.467	0.25
60	21	0.35	0.231	0.484	0.253
60	22	0.367	0.246	0.501	0.255

Table 10 Estimates and 95% CIs with 75 PD-L1 Strongly Positive Subjects

Sample Size	Number of ORR Event	Proportion	Lower Limit	Upper Limit	Width of 95% CI
75	20	0.267	0.171	0.381	0.21
75	21	0.280	0.182	0.396	0.214
75	22	0.293	0.194	0.41	0.216
75	23	0.307	0.205	0.424	0.219
75	24	0.320	0.217	0.438	0.221
75	25	0.333	0.229	0.452	0.223
75	26	0.347	0.24	0.465	0.225
75	27	0.360	0.252	0.479	0.227
75	28	0.373	0.264	0.493	0.229
75	29	0.387	0.276	0.506	0.23
75	30	0.400	0.288	0.52	0.232

Up to 350 subjects will be enrolled. Assuming a 33% prevalence rate of PD-L1 strongly positive subjects and 100 for biomarker discovery population, there is 88% chance to have at least 75 PD-L1 strongly positive subjects and 99.9% chance to have at least 60 PD-L1 strongly positive subjects in the confirmation group.

For all and PD-L1 positive subjects, the expected sample sizes (350 and 225, respectively) are adequate for efficacy estimation. Thus, if strongly PD-L1 positive cannot be determined, the study may stop enrollment after ~225 subjects are enrolled.

8.2.8 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables for all subjects, PD-L1 positive subjects, and PD-L1 strongly positive subjects, respectively:

- Age category (≤ 65 vs. > 65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- ECOG status (0 / 1 vs. 2 and 0 vs 1 / 2)
- Geographic region of enrolling site (East Asia vs. non-East Asia and EU vs. non-EU)
- Presence or absence of liver metastases at baseline
- Baseline hemoglobin (≥ 10 g/dL vs. < 10 g/dL)
- Naïve vs. prior adjuvant/neoadjuvant chemotherapy
- Bajorin risk score

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.2.9 Interim Analyses

A biomarker analysis is planned where data from a subset of subjects (the biomarker discovery population) will be used to determine the PD-L1 strongly positive cut-point. The biomarker discovery population consists of the evaluable subjects among the first 100 subjects enrolled into the study. Analysis will be conducted according to the SAP (section 8.2.5.3). More subjects may be allocated to the biomarker discovery population, if necessary.

In addition, an interim efficacy evaluation for the PD-L1 negative population will be performed using the biomarker discovery population data. Enrollment of PD-L1 negative (CPS $< 1\%$) population may be stopped if the ORR is low and substantial enrollment remains. The futility analysis will be based on the evaluable PD-L1 negative subjects in the biomarker discovery population (up to the first 25 subjects). If the number of PD-L1 negative subjects in the biomarker subgroup is less than 20, additional PD-L1 negative subjects may be included until the number reaches at least 20. The non-binding rule for futility is the upper limit of the 95% CI (two-sided) of the ORR estimate is less than 20% (need at least 1 response in $N < 26$ subjects, and at least 2 responses in $N=26$ to 40 subjects).

8.2.10 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives the study medication infusion. The number of Days on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication.

Summary statistics for the number of Days on Therapy will be provided by treatment group for the APT population.

8.2.11 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for the APT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in [Table 11](#).

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab (MK-3475) 100 mg / 4mL	Solution for Infusion

9.2 Packaging and Labeling Information

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

All supplies will be provided open label. Pembrolizumab (MK-3475) will be provided as non-kitted single vials or as single vials in a kit box.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees

to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The DNA and tumor tissue specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA and tumor tissue 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.

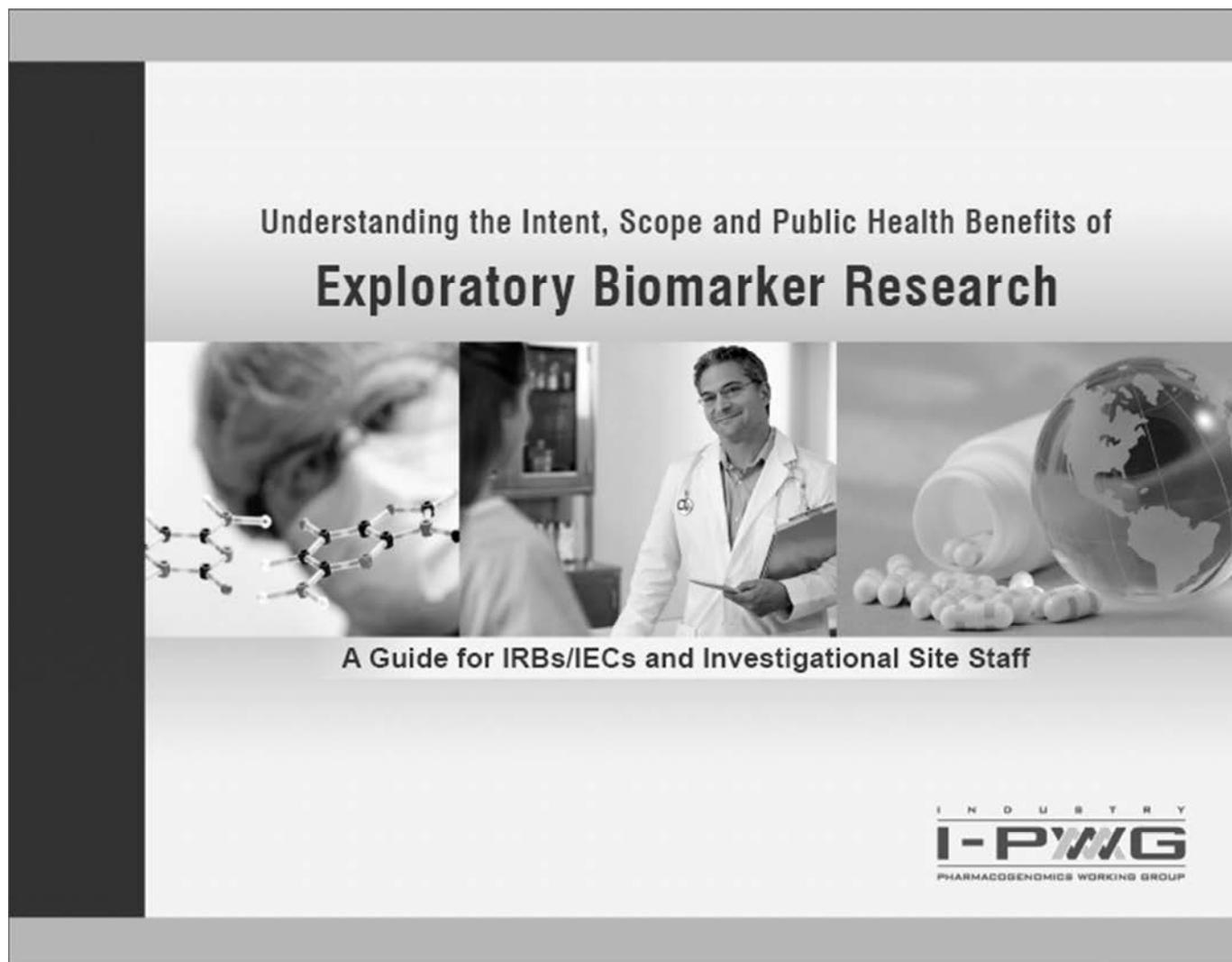
13. Questions

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 Brochure² and ICH Guidance E15³ 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.

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.

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.²⁶ 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 (Erbix[®]) 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 sur-

rogates 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

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.²⁶⁻³¹

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

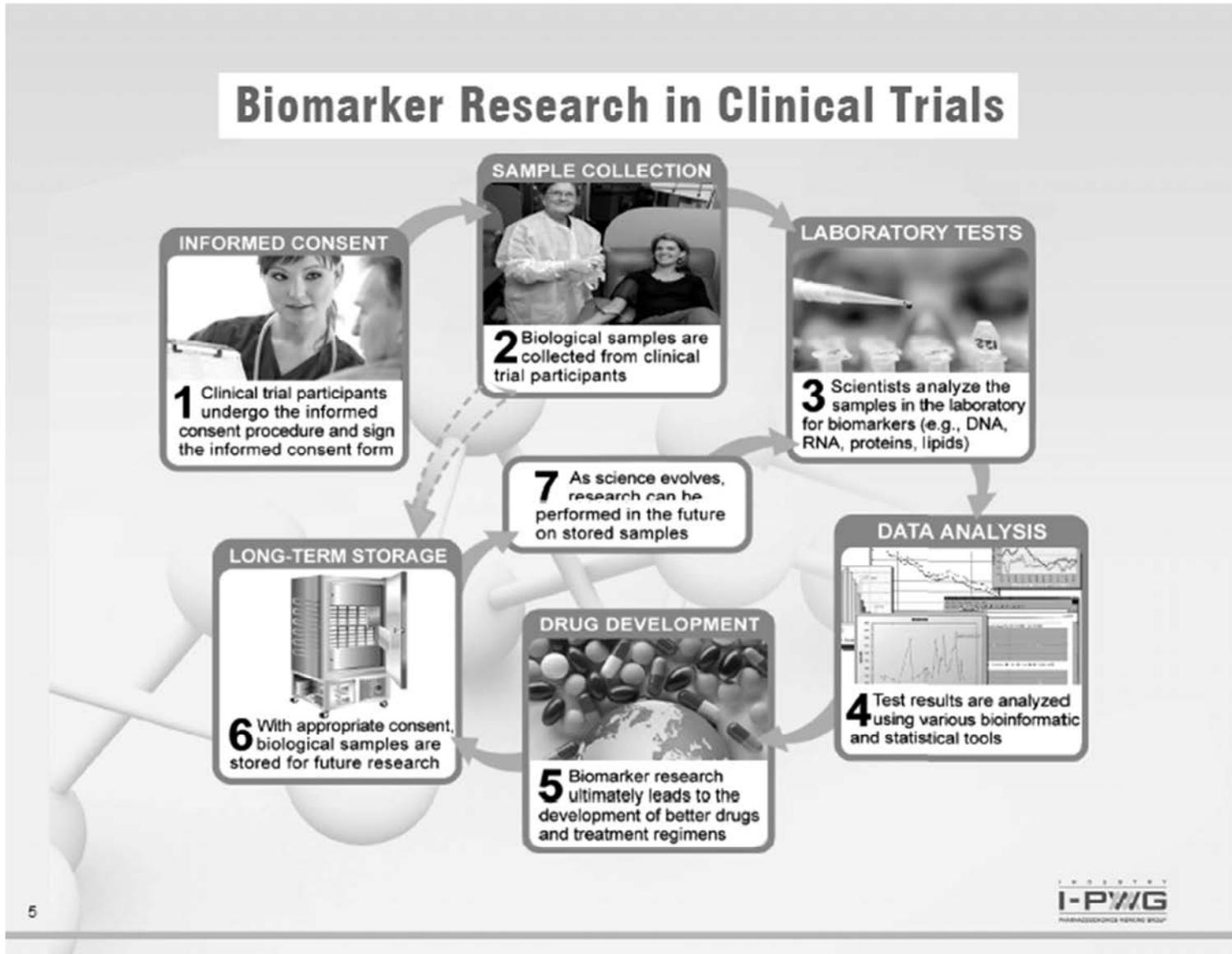
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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.



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.³⁴⁻³⁶

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 (Erbix[®]) 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

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-

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

14. Contributing authors

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9





12.4 Abbreviations

Abbreviation/Term	Definition
1L	First Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APaT	All Patients as Treated
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
β-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DAP	Data Analysis Plan
DNA	Deoxyribonucleic acid
DR	Drug Related
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin Fixed Paraffin Embedded

Abbreviation/Term	Definition
FNA	Fine Needle Aspirate
GC	Gemcitabine/Carboplatin
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HEA	Health Economic Assessment
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
KM	Kaplan-Meier
mAb	Monoclonal Antibody
mcL	Microliters
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective response Rate

Abbreviation/Term	Definition
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival
PGt	Pharmacogenetic
PIN	Personal Identification Number
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PT	Prothrombin Time
PS	Performance Status
QoL	Quality of Life
R/M	Recurrent or Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SFU	Survival Follow-Up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SOP	Standard Operating Procedures
T3	Total triiodothyronine
T4	Free tyroxine
TIL	Tumor Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
V-type	Ig Variable-type
WBC	White Blood Cell

12.5 ECOG Performance Status

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.
<p>* As published in Am. J. Clin. Oncol.: <i>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.</i> The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.</p>	

12.6 New York Heart Association (NYHA) Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.
<i>* As published in: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.</i>	

12.7 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>).

12.8 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria For Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

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	